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=> s herpesvirus entry mediator
L1          237 HERPESVIRUS ENTRY MEDIATOR

=> s l1 and "HVEM"
L2           96 L1 AND "HVEM"

=> dup remove l2
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PROCESSING COMPLETED FOR L2
L3 39 DUP REMOVE L2 (57 DUPLICATES REMOVED)

=> s l3 and inhibit proliferation
L4 0 L3 AND INHIBIT PROLIFERATION

=> d l3 1-39 cbib abs

L3 ANSWER 1 OF 39 MEDLINE DUPLICATE 1
2002111908 Document Number: 21826705. PubMed ID: 11836420. Effects of herpes simplex virus on structure and function of nectin-1/HveC. Krummenacher Claude; Baribaud Isabelle; Sanzo James F; Cohen Gary H; Eisenberg Roselyn J. (Department of Microbiology, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA.. krumm@biochem.dental.upenn.edu) . JOURNAL OF VIROLOGY, (2002 Mar) 76 (5) 2424-33. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.
AB Herpes simplex virus (HSV) entry requires the interaction between the envelope glycoprotein D (gD) and a cellular receptor such as nectin-1 (also named **herpesvirus entry mediator** C [HveC]) or HveA/**HVEM**. Nectin-1 is a cell adhesion molecule found at adherens junctions associated with the cytoplasmic actin-binding protein afadin. Nectin-1 can act as its own ligand in a homotypic interaction to bridge cells together. We used a cell aggregation assay to map an adhesive functional site on nectin-1 and identify the effects of gD binding and HSV early infection on nectin-1 function. Soluble forms of nectin-1 and anti-nectin-1 monoclonal antibodies were used to map a functional adhesive site within the first immunoglobulin-like domain (V domain) of nectin-1. This domain also contains the gD-binding site, which appeared to overlap the adhesive site. Thus, soluble forms of gD were able to prevent nectin-1-mediated cell aggregation and to disrupt cell clumps in an affinity-dependent manner. HSV also prevented nectin-1-mediated cell aggregation by occupying the receptor. Early in infection, nectin-1 was not downregulated from the cell surface. Rather, detection of nectin-1 changed gradually over a 30-min period of infection, as reflected by a decrease in the CK41 epitope and an increase in the CK35 epitope. The level of detection of virion gD on the cell surface increased within 5 min of infection in a receptor-dependent manner. These observations suggest that cell surface nectin-1 and gD may undergo conformational changes during HSV entry as part of an evolving interaction between the viral envelope and the cell plasma membrane.

L3 ANSWER 2 OF 39 MEDLINE DUPLICATE 2
2002045584 Document Number: 21629477. PubMed ID: 11756979. Search for polymorphisms in the genes for **herpesvirus entry mediator**, nectin-1, and nectin-2 in immune seronegative individuals. Struyf Frank; Posavad Christine M; Keyaerts Els; Van Ranst Marc; Corey Lawrence; Spear Patricia G. (Department of Microbiology-Immunology, Northwestern University Medical School, Chicago, Illinois 60611, USA.) JOURNAL OF INFECTIOUS DISEASES, (2002 Jan 1) 185 (1) 36-44. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.
AB Recently, individuals have been identified who possess T cell responses to herpes simplex virus (HSV) antigens despite the absence of detectable anti-HSV antibodies in their serum. The significance of this immune seronegative status is unclear, but it could indicate resistance to overt HSV infection. The aims of the present study were to investigate whether genetic differences in receptors used by HSV for cell entry (**herpesvirus entry mediator [HVEM]**, nectin-1, and nectin-2) could be detected in immune seronegative individuals. Coding polymorphisms were identified in the **HVEM** and nectin-1 genes. The variant receptor proteins were expressed, and their ability to bind the viral ligand glycoprotein D and to mediate HSV entry after transient transfection into normally resistant cells was compared with that of their wild-type counterparts. HSV entry activity in

wild-type and variant forms of the receptors was indistinguishable, which indicates that the polymorphisms observed are unlikely to explain the possible restrictions on HSV replication or spread in immune seronegative individuals.

L3 ANSWER 3 OF 39 CAPLUS COPYRIGHT 2002 ACS
2001:598037 Document No. 135:179726 Identification of a novel domain in the tumor necrosis factor receptor family that mediates pre-ligand receptor assembly and function. Lenardo, Michael J.; Chan, Francis Ka-ming; Siegel, Richard M. (Government of the United States of America as Represented by the Secretary, Department of Health and Human Services, USA). PCT Int. Appl. WO 2001058953 A2 20010816, 77 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US4125 20010209. PRIORITY: US 2000-PV181909 20000211.
AB The authors disclose the identification and characterization of an amino acid sequence termed PLAD (pre-ligand assembly domain) found in the extracellular domains of the TNF receptor superfamily. In one example, self-assocn. of the p60 and p80 receptor monomers was demonstrated to occur in the absence of the TNF-.alpha. ligand. In a second example using wild-type and engineered constructs of CD95, the apoptotic signaling function was shown to correlate with the ability to self-assoc. independent of ligand binding.

L3 ANSWER 4 OF 39 CAPLUS COPYRIGHT 2002 ACS
2001:338564 Document No. 134:348630 New members of the TRAF (tumor necrosis factor receptor-associated factor) protein family with possible therapeutic uses. Zapata, Juan M.; Reed, John C. (The Burnham Institute, USA). PCT Int. Appl. WO 2001032696 A2 20010510, 156 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US30533 20001103. PRIORITY: US 1999-434784 19991105.
AB In accordance with the present invention, there are provided novel TRAF-Protein-Binding-Domain polypeptides (TPBDs). The invention also provides nucleic acid mols. encoding TPBDs, vectors contg. these nucleic acid mols. and host cells contg. the vectors. The invention also provides antibodies that can specifically bind to invention TPBDs. Such TPBDs and/or anti-TPBD antibodies are useful for discovery of drugs that suppress autoimmunity, inflammation, allergy, allograft rejection, sepsis, and other diseases. Characterization of the proteins is reported and their interaction of other members of the family. A reporter gene assay for measuring their effects on NF-.kappa.B activity is described.

L3 ANSWER 5 OF 39 CAPLUS COPYRIGHT 2002 ACS
2001:354356 Document No. 135:120439 Alterations of gene expression during colorectal carcinogenesis revealed by cDNA microarrays after laser-capture microdissection of tumor tissues and normal epithelia. Kitahara, Osamu; Furukawa, Yoichi; Tanaka, Toshihiro; Kihara, Chikashi; Ono, Kenji; Yanagawa, Renpei; Nita, Marcelo E.; Takagi, Toshihisa; Nakamura, Yusuke; Tsunoda, Tatsuhiko (Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo, 108-8639, Japan). Cancer Research, 61(9), 3544-3549 (English) 2001. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.

AB To identify a set of genes involved in the development of colorectal carcinogenesis, we compared expression profiles of colorectal cancer cells from eight tumors with corresponding noncancerous colonic epithelia using a DNA microarray consisting of 9216 human genes. These cell populations had been rendered homogeneous by laser-capture microdissection. Expression change in more than half of the tumors was obsd. for 235 genes, i.e., 44 up-regulated and 191 down-regulated genes. The differentially expressed genes include those assocd. with signal transduction, metabolizing enzymes, prodn. of reactive oxygen species, cell cycle, transcription, mitosis, and apoptosis. Subsequent examn. of 10 genes (five up-regulated and five down-regulated) by semiquant. reverse transcription-PCR using the eight tumors together with an addnl. 12 samples substantiated the reliability of our anal. The extensive list of genes identified in these expts. provides a large body of potentially valuable information of colorectal carcinogenesis and represents a source of novel targets for cancer therapy.

L3 ANSWER 6 OF 39 MEDLINE DUPLICATE 3
2001680220 Document Number: 21583213. PubMed ID: 11726199. LIGHT, a member of the TNF superfamily, induces morphological changes and delays proliferation in the human rhabdomyosarcoma cell line RD. Hikichi Y; Matsui H; Tsuji I; Nishi K; Yamada T; Shintani Y; Onda H. (Discovery Research Laboratories I, Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 10 Wadai, Tsukuba, Ibaraki 300-4293, Japan.) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2001 Dec 7) 289 (3) 670-7. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB LIGHT is a member of the tumor necrosis factor (TNF) superfamily, which binds two known receptors, lymphotoxin-beta receptor (LTbetaR) and the **herpesvirus entry mediator** (**HVEM**)/TR2. We investigated the effects of LIGHT on the human rhabdmyosarcoma cell line RD. LIGHT delayed cell proliferation and induced morphological changes of the cells. These effects were not shown by other TNF family ligands such as TNFalpha and LTalpha, which induced the transcriptional activity of nuclear factor-kappaB (NF-kappaB) and NF-kappaB-responsible chemokine productions in the same manner as did LIGHT. LTalpha1beta2, another TNF family ligand for LTbetaR, was shown to have similar activities in RD cells as LIGHT. Both LIGHT and LTalpha1beta2 induced the expression of muscle-specific genes such as smooth muscle (SM) alpha-actin, while TNFalpha and LTalpha did not. These findings indicate that LIGHT may be a novel inducer of RD cell differentiation associated with SM alpha-actin expression through the LTbetaR.

L3 ANSWER 7 OF 39 MEDLINE DUPLICATE 4
2001371428 Document Number: 21322536. PubMed ID: 11429164. Recombinant, soluble LIGHT (**HVEM** ligand) induces increased IL-8 secretion and growth arrest in A375 melanoma cells. Hehlgans T; Mannel D N. (Institute of Pathology/Tumor Immunology, University of Regensburg, F.-J.-Strauss-Allee 11, D-93042 Regensburg, Germany.) JOURNAL OF INTERFERON AND CYTOKINE RESEARCH, (2001 May) 21 (5) 333-8. Journal code: CD4; 9507088. ISSN: 1079-9907. Pub. country: United States. Language: English.

AB The heterotrimeric lymphotoxin alpha(1)beta(2) (LTalpha(1)beta(2)) complex and LIGHT, a new member of the tumor necrosis factor (TNF) superfamily, have been identified as membrane-anchored ligands for the LTbeta receptor (LTbetaR), a member of the TNF receptor (TNFR) superfamily. Although some of the biologic activities of this receptor have been described using either soluble LTalpha(1)beta(2) as a ligand or agonistic monoclonal antibodies (mAb), very little is known about the signaling of LIGHT via the LTbetaR. To gain more insight into the biologic functions of LIGHT, we generated a recombinant soluble form of human LIGHT (rsHuLIGHT). We demonstrate here that this rsHuLIGHT is capable of binding to the LTbetaR. Interestingly, receptor-mediated ligand precipitation analysis revealed that rsHuLIGHT bound only to human LTbetaR but not to mouse LTbetaR,

indicating a species-specific receptor ligand interaction. Activation of A375 human melanoma cells by rsHuLIGHT induced an increased secretion of interleukin-8 (IL-8). Furthermore, rsHuLIGHT caused growth arrest of A375 cells even in the absence of interferon-gamma (IFN-gamma).

L3 ANSWER 8 OF 39 SCISEARCH COPYRIGHT 2002 ISI (R)
2001:643595 The Genuine Article (R) Number: 460JQ. TNF-alpha receptor 1 (p55) on islets is necessary for the expression of LIGHT on diabetogenic T cells . Pakala S V (Reprint); Ilic A; Chen L P; Sarvetnick N. Scripps Clin & Res Inst, Dept Immunol, 10550 N Torrey Pines Rd, La Jolla, CA 92037 USA (Reprint); Scripps Clin & Res Inst, Dept Immunol, La Jolla, CA 92037 USA; Mayo Clin, Dept Immunol, Rochester, MN 55905 USA. CLINICAL IMMUNOLOGY (AUG 2001) Vol. 100, No. 2, pp. 198-207. Publisher: ACADEMIC PRESS INC. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA. ISSN: 1521-6616. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Insulin-dependent diabetes mellitus results from T-cell-mediated destruction of pancreatic islet beta cells. Both CD4 and CD8 T cells have been shown to be independently capable of beta cell destruction. However, the mechanism of beta cell destruction has remained elusive. It has previously been shown that the absence of TNF-alpha receptor 1 (p55) on the islets protected islets from CD4 T-cell-mediated destruction as long as the T cells did not have access to wild-type islets in vivo. Wild-type and TNF-alpha receptor 1 (p55) deficient islets induce similar levels of proliferation of BDC2.5 T cells. In this study, we demonstrate that islet TNF-alpha receptor I (p55) influences the expression of LIGHT (TNFSF-14), a TNF family member with both cytolytic and costimulatory properties, on BDC2.5 T cells and the expression of its receptor **HVEM** (TNFRSF-14) by islets, indicating a role for LIGHT-**HVEM** interactions in autoimmune diabetes. (C) 2001 Academic Press.

L3 ANSWER 9 OF 39 CAPLUS COPYRIGHT 2002 ACS
2000:421293 Document No. 133:57683 A method of manufacturing active lymphotoxin-.beta. receptor immunoglobulin chimeric proteins. Browning, Jeffrey; Miatkowski, Konrad; Meier, Werner (Biogen, Inc., USA). PCT Int. Appl. WO 2000036092 A2 20000622, 45 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US29873 19991216. PRIORITY: US 1998-PV112752 19981217.
AB Methods for high level expression of active lymphotoxin-.beta. receptor Ig chimeric proteins (LT.beta.R-Ig) and their purifn. are provided. The chimeric protein LT.beta.R-Ig contg. the ligand binding domain of lymphotoxin-.beta. receptor and Ig Fc domain linked by a spacer peptide are expressed in CHO cells and other protein expression systems. To increase the percentage of properly folded protein (live form), low temp. fermn. conditions are used. Hinge modification by site-specific mutagenesis to replace Cys101 and Cys108 to Ala in Ig Fc domain is also used to correct the folding problems of the fusion protein. Conventional hydrophobic interaction chromatog. can be used to sep. and quantitate the live proteins and dead proteins (protein mols. with ligand binding affinity substantially (10-1000 fold) lower than the natural or active form). The live protein can also be purified by monoclonal antibody affinity column. The analyses of purified secreted LT.beta.R-Ig or **HVEM** (**Herpesvirus entry mediator**) -Ig and their ligand binding activities are presented.

L3 ANSWER 10 OF 39 CAPLUS COPYRIGHT 2002 ACS
2000:175929 Document No. 132:218642 Novel molecules of the herpes virus-entry-mediator-related protein family and their diagnostic and

therapeutic uses. Busfield, Samantha J. (Millennium Biotherapeutics, Inc., USA). PCT Int. Appl. WO 2000014230 A1 20000316, 151 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US20180 19990903. PRIORITY: US 1998-146950 19980903; US 1999-342767 19990629.

AB The present invention is based on the discovery of 3 cDNA mols. which encode sol. forms (sHVEM), and one cDNA mol. that encodes a second membrane-bound form, of the membrane-bound herpes virus entry mediator (mHVEM), a member of the tumor necrosis factor receptor superfamily. The 3 sHVEM sequences differ from mHVEM in 2 important ways: first they lac the C-terminal end of mHVEM which contains the transmembrane domain of mHVEM; and secondly, they have addnl. amino acids at their C-terminal ends that are not found at the C-terminal end of mHVEM. The **HVEM** mols. bind to LIGHT (also called TANGO-69) and lymphotoxin a, such that the mols. are also known as TANGO-69 receptors. Northern blot anal. revealed that an .apprx.2 kb sHVEM1 mRNA transcript is present at similar levels in stimulated and unstimulated mast cells, as well as in stimulated human umbilical vein endothelial cells (HUVECs), but not in unstimulated HUVECs. Tissue localization suggests that sHVEM1 can play a role in allergic reactions and can play an anti-inflammatory role in the endothelium. Mapping data places TANGO-69 receptor gene at human chromosome 1 region p36.2-p36.3, an area putatively syntenic to a region of mouse chromosome 4 near the IgE defective response locus. In addn. to isolated, full-length TANGO-69-receptor proteins, the invention further provides isolated TANGO-69-receptor fusion proteins, antigenic peptides and anti-TANGO-69-receptor antibodies. The invention also provides TANGO-69-receptor nucleic acid mols., recombinant expression vectors contg. a nucleic acid mol. of the invention, host cells into which the expression vectors have been introduced and non-human transgenic animals in which a TANGO-69-receptor gene has been introduced or disrupted. Diagnostic, screening and therapeutic methods utilizing compns. of the invention are also provided.

L3 ANSWER 11 OF 39 SCISEARCH COPYRIGHT 2002 ISI (R)

2000:943983 The Genuine Article (R) Number: 381AH. Overexpression of Bcl-2 enhances LIGHT- and interferon-gamma-mediated apoptosis in Hep3BT2 cells. Chen M C; Hsu T L; Luh T Y; Hsieh S L (Reprint). NATL YANG MING UNIV, INST MICROBIOL & IMMUNOL, TAIPEI 11221, TAIWAN (Reprint); NATL YANG MING UNIV, INST MICROBIOL & IMMUNOL, TAIPEI 11221, TAIWAN; NATL YANG MING UNIV, DEPT IMMUNOL & MICROBIOL, TAIPEI 11221, TAIWAN; NATL TAIWAN UNIV, DEPT CHEM, TAIPEI 11221, TAIWAN; NATL YANG MING UNIV, IMMUNOL RES CTR, TAIPEI 11221, TAIWAN. JOURNAL OF BIOLOGICAL CHEMISTRY (8 DEC 2000) Vol. 275, No. 49, pp. 38794-38801. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. ISSN: 0021-9258. Pub. country: TAIWAN. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB LIGHT is a member of the tumor necrosis factor superfamily and is the Ligand for LT-betaR, **HVEM**, and decoy receptor 3. LIGHT has a cytotoxic effect, which is further enhanced by the presence of interferon-gamma (IFN-gamma). Although LIGHT/IFN-gamma can activate caspase activity, neither benzyloxycarbonyl-Asp-Glu-Val-Asp-fluoromethylketone nor benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone can completely inhibit LIGHT/IFN-gamma -mediated apoptosis. Moreover, overexpression of Bcl-2 further enhances LIGHT/IFN-gamma -mediated apoptosis. It appears that LIGHT and IFN-gamma act synergistically to activate caspase-3, with the resultant cleavage of Bcl-2, removal of the BH4 domain, leading to conversion of Bcl-2 from an antiapoptotic to a proapoptotic form in p53-deficient hepatocellular carcinoma Hep3BT2 cells. Thus, LIGHT seems to be able to override the protective effect of Bcl-2

and induce cell death. Although benzyloxycarbonyl-Asp-Glu-Val-Asp-fluoromethylketone and benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone can prevent the cleavage of Bcl-2 by LIGHT/IFN-gamma they only partially inhibit apoptosis in Hep3BT2 cells that are overexpressing Bcl-2. In contrast, both LIGHT/IFN-gamma -mediated apoptosis and Bcl-2 cleavage are inhibited by free radical scavengers, indicating that free radicals may play an essential role in LIGHT/IFN-gamma -mediated apoptosis at a step upstream of caspase-3 activation. These results suggest that LIGHT signaling may diverge into multiple, separate processes.

L3 ANSWER 12 OF 39 MEDLINE
2000487952 Document Number: 20491929. PubMed ID: 11035077. Reciprocal expression of the TNF family receptor herpes virus entry mediator and its ligand LIGHT on activated T cells: LIGHT down-regulates its own receptor. Morel Y; Schiano de Colella J M; Harrop J; Deen K C; Holmes S D; Wattam T A; Khandekar S S; Truneh A; Sweet R W; Gastaut J A; Olive D; Costello R T. (Laboratoire d'Immunologie des Tumeurs, Departement d'Hematologie, Institut Paoli Calmettes, Universite de la Mediterranee, Marseille, France.) JOURNAL OF IMMUNOLOGY, (2000 Oct 15) 165 (8) 4397-404. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The TNF receptor (TNFR) family plays a central role in the development of the immune response. Here we describe the reciprocal regulation of the recently identified TNFR superfamily member herpes virus entry mediator (**HVEM**) (TR2) and its ligand LIGHT (TL4) on T cells following activation and the mechanism of this process. T cell activation resulted in down-regulation of **HVEM** and up-regulation of LIGHT, which were both more pronounced in CD8(+) than CD4(+) T lymphocytes. The analysis of **HVEM** and LIGHT mRNA showed an increase in the steady state level of both mRNAs following stimulation. LIGHT, which was present in cytoplasm of resting T cells, was induced both in cytoplasm and at the cell surface. For **HVEM**, activation resulted in cellular redistribution, with its disappearance from cell surface. **HVEM** down-regulation did not rely on de novo protein synthesis, in contrast to the partial dependence of LIGHT induction. Matrix metalloproteinase inhibitors did not modify **HVEM** expression, but did enhance LIGHT accumulation at the cell surface. However, **HVEM** down-regulation was partially blocked by a neutralizing mAb to LIGHT or an **HVEM** -Fc fusion protein during activation. As a model, we propose that following stimulation, membrane or secreted LIGHT binds to **HVEM** and induces receptor down-regulation. Degradation or release of LIGHT by matrix metalloproteinases then contributes to the return to baseline levels for both LIGHT and **HVEM**. These results reveal a self-regulating ligand/receptor system that contributes to T cell activation through the interaction of T cells with each other and probably with other cells of the immune system.

L3 ANSWER 13 OF 39 MEDLINE DUPLICATE 5
2000219245 Document Number: 20219245. PubMed ID: 10754304. LIGHT, a TNF-like molecule, costimulates T cell proliferation and is required for dendritic cell-mediated allogeneic T cell response. Tamada K; Shimozaki K; Chapoval A I; Zhai Y; Su J; Chen S F; Hsieh S L; Nagata S; Ni J; Chen L. (Department of Immunology, Mayo Graduate and Medical Schools, Mayo Clinic, Rochester, MN 55905, USA.) JOURNAL OF IMMUNOLOGY, (2000 Apr 15) 164 (8) 4105-10. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB LIGHT is a recently identified member of the TNF superfamily and its receptors, **herpesvirus entry mediator** and lymphotoxin beta receptor, are found in T cells and stromal cells. In this study, we demonstrate that LIGHT is selectively expressed on immature dendritic cells (DCs) generated from human PBMCs. In contrast, LIGHT is not detectable in DCs either freshly isolated from PBMCs or rendered mature in vitro by LPS treatment. Blockade of LIGHT by its soluble receptors, lymphotoxin beta receptor-Ig or **HVEM**-Ig, inhibits the induction of DC-mediated primary allogeneic T cell response. Furthermore,

engagement of LIGHT costimulates human T cell proliferation, amplifies the NF-kappaB signaling pathway, and preferentially induces the production of IFN-gamma, but not IL-4, in the presence of an antigenic signal. Our results suggest that LIGHT is a costimulatory molecule involved in DC-mediated cellular immune responses.

L3 ANSWER 14 OF 39 SCISEARCH COPYRIGHT 2002 ISI (R)
2000:563627 The Genuine Article (R) Number: 336GP. Chronic lymphocytic leukemia B cells are highly sensitive to infection by herpes simplex virus-1 via **herpesvirus-entry-mediator** A.
Eling D J; Johnson P A; Sharma S; Tufaro F; Kipps T J (Reprint). UNIV CALIF SAN DIEGO, DEPT MED, DIV HEMATOL ONCOL, SCH MED, 9500 GILMAN DR, LA JOLLA, CA 92093 (Reprint); UNIV CALIF SAN DIEGO, DEPT MED, DIV HEMATOL ONCOL, SCH MED, LA JOLLA, CA 92093; NEUROVIR THERAPEUT INC, VANCOUVER, BC, CANADA. GENE THERAPY (JUL 2000) Vol. 7, No. 14, pp. 1210-1216. Publisher: NATURE PUBLISHING GROUP. HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND. ISSN: 0969-7128. Pub. country: USA; CANADA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB We found that chronic lymphocytic leukemic (CLL) B cells are highly sensitive to infection with vectors derived from replication-defective herpes simplex virus-1 (rdHSV-1). CLL B cells were found to express high levels of herpes virus entry mediator (Hve) A, but not HveC, the other known receptor for HSV-1. An HveA cDNA from CLL cells was found to encode Arg-Lys and Val->lso substitutions at amino acids 17 and 241, respectively. Nevertheless, this cDNA encoded a functional receptor for HSV-I when transfected into Chinese hamster ovarian (CHO) cells. Antibodies to HveA could block rdHSV-1 infection of CLL cells and HveA-transfected CHO cells with similar efficiencies in vitro. In contrast to B cells of normal donors, CLL B cells were resistant to the cytopathic effects of infection by rdHSV-1 and maintained high-level expression of the transgene for several days in vitro. We propose that this is due to the expression by CLL cells of the anti-apoptotic protein, bcl-2. Consistent with this, we found that transduction of HeLa cells with a retrovirus expression vector encoding bcl-2 rendered HeLa cells resistant to the cytopathic effects of rdHSV-1. HSV-1-derived vectors should be excellent vehicles for gene transfer into CLL B cells, allowing for its potential use in gene therapy for this disease.

L3 ANSWER 15 OF 39 CAPLUS COPYRIGHT 2002 ACS
1999:286084 Document No. 130:307554 Human herpesvirus receptor cDNA and cells expressing it and their use in antiviral drug screening. Fuller, A. Oveta; Li, Qing-Xue; McLaren, Ning-Hun C.; Perez, Aleida; Subramanian, Gangadharan (The Regents of the University of Michigan, USA). PCT Int. Appl. WO 9920761 A2 19990429, 89 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US22342 19981022. PRIORITY: US 1997-955531 19971022.
AB The invention provides compns. and methods for identifying and testing therapeutics against HSV infection, and in particular, compns. comprising receptors which enable cell-specific entry of HSV. The invention also provides a novel DNA sequence that encodes a protein B5T74 that confers the ability of herpes simplex virus (HSV) to infect and replicate in otherwise non-permissive cells. Also provided are vectors comprising the DNA and a porcine cell system which expresses a herpes simplex virus receptor, but does not express endogenous, HSV entry receptors. Thus, screening of a human cDNA library for DNA conferring HSV susceptibility on porcine SK6-A7 cells yielded two cDNAs, i.e., one encoding known **HVEM** protein and another encoding an unrelated 42.5 kilodalton protein. The latter protein, which appeared to be a type II transmembrane protein, was unrelated to CD30, CD40 and HFAS as well as **HVEM**.

Expts. with **HVEM**-expressing porcine cells (HB1-9) indicated that **HVEM**, gD and gH interacted in the process of HSV entry into the recombinant cells.

L3 ANSWER 16 OF 39 MEDLINE DUPLICATE 6
1999253915 Document Number: 99253915. PubMed ID: 10318773. A newly identified member of tumor necrosis factor receptor superfamily (TR6) suppresses LIGHT-mediated apoptosis. Yu K Y; Kwon B; Ni J; Zhai Y; Ebner R; Kwon B S. (Department of Microbiology and Immunology and Walther Oncology Center, Indiana University School of Medicine and the Walther Cancer Institute, Indianapolis, Indiana 46202, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 May 14) 274 (20) 13733-6. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB TR6 (decoy receptor 3 (DcR3)) is a new member of the tumor necrosis factor receptor (TNFR) family. TR6 mRNA is expressed in lung tissues and colon adenocarcinoma, SW480. In addition, the expression of TR6 mRNA was shown in the endothelial cell line and induced by phorbol 12-myristate 13-acetate/ionomycin in Jurkat T leukemia cells. The open reading frame of TR6 encodes 300 amino acids with a 29-residue signal sequence but no transmembrane region. Using histidine-tagged recombinant TR6, we screened soluble forms of TNF-ligand proteins with immunoprecipitation. Here, we demonstrate that TR6 specifically binds two cellular ligands, LIGHT (herpes virus entry mediator (**HVEM**)-L) and Fas ligand (FasL/CD95L). These bindings were confirmed with HEK 293 EBNA cells transfected with LIGHT cDNA by flow cytometry. TR6 inhibited LIGHT-induced cytotoxicity in HT29 cells. It has been shown that LIGHT triggers apoptosis of various tumor cells including HT29 cells that express both lymphotoxin beta receptor (LTbetaR) and **HVEM**/TR2 receptors. Our data suggest that TR6 inhibits the interactions of LIGHT with **HVEM** /TR2 and LTbetaR, thereby suppressing LIGHT- mediated HT29 cell death. Thus, TR6 may play a regulatory role for suppressing in FasL- and LIGHT-mediated cell death.

L3 ANSWER 17 OF 39 SCISEARCH COPYRIGHT 2002 ISI (R)
1999:410801 The Genuine Article (R) Number: 198QZ. Tumor necrosis factor receptor and Fas signaling mechanisms. Wallach D (Reprint); Varfolomeev E E; Malinin N L; Goltsev Y V; Kovalenko A V; Boldin M P. WEIZMANN INST SCI, DEPT BIOL CHEM, IL-76100 REHOVOT, ISRAEL (Reprint). ANNUAL REVIEW OF IMMUNOLOGY (4 JUN 1999) Vol. 17, pp. 331-367. Publisher: ANNUAL REVIEWS INC. 4139 EL CAMINO WAY, PO BOX 10139, PALO ALTO, CA 94303-0139. ISSN: 0732-0582. Pub. country: ISRAEL. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Four members of the tumor necrosis factor (TNF) ligand family, TNF-alpha, LT-alpha, LT-beta, and LIGHT, interact with four receptors of the TNF/nerve growth factor family, the p55 TNF receptor (CD120a), the p75 TNF receptor (CD120b), the lymphotoxin beta receptor (LT beta R), and herpes virus entry mediator (**HVEM**) to control a wide range of innate and adaptive immune response functions. Of these, the most thoroughly studied are cell death induction and regulation of the inflammatory process. Fas/Apo1 (CD95), a receptor of the TNF receptor family activated by a distinct ligand, induces death in cells through mechanisms shared with CD120a. The last four years have seen a proliferation in knowledge of the proteins participating in the signaling by the TNF system and CD95. The downstream signaling molecules identified so far-caspases, phospholipases, the three known mitogen activated protein (MAP) kinase pathways, and the NF-kappa B activation cascade-mediate the effects of other inducers as well. However, the molecules that initiate these signaling events, including the death domain- and TNF receptor associated factor (TRAF) domain-containing adapter proteins and the signaling enzymes associated with them, are largely unique to the TNF/nerve growth factor receptor family.

L3 ANSWER 18 OF 39 SCISEARCH COPYRIGHT 2002 ISI (R)
1999:680584 The Genuine Article (R) Number: 231EN. A homogenous 384-well high throughput screen for novel tumor necrosis factor receptor: Ligand

interactions using time resolved energy transfer. Moore K J; Turconi S; MilesWilliams A; Djaballah H; Hurskainen P; Harrop J; Murray K J; Pope A J (Reprint). SMITHKLINE BEECHAM PHARMACEUT, DEPT MOL SCREENING TECHNOL, NEW FRONTIER SCI PK N, 3RD AVE, HARLOW CM19 5AW, ESSEX, ENGLAND (Reprint); SMITHKLINE BEECHAM PHARMACEUT, DEPT MOL SCREENING TECHNOL, HARLOW CM19 5AW, ESSEX, ENGLAND; SMITHKLINE BEECHAM PHARMACEUT, DEPT IMMUNOL, HARLOW CM19 5AW, ESSEX, ENGLAND; WALLAC OY, TURKU, FINLAND. JOURNAL OF BIOMOLECULAR SCREENING (AUG 1999) Vol. 4, No. 4, pp. 205-214. Publisher: MARY ANN LIEBERT INC PUBL. 2 MADISON AVENUE, LARCHMONT, NY 10538. ISSN: 1087-0571. Pub. country: ENGLAND; FINLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The herpes virus entry mediator (**HVEM**) receptor and its ligand, **HVEM**-L, are involved in both herpes simplex virus type-1 (HSV-1) herpes simplex virus type-2 (HSV-2) infection, and in T-cell activation such that antagonists of this interaction are expected to have utility in viral and inflammatory diseases, In this report we describe the configuration of a homogeneous 384-well assay based on time-resolved energy transfer from a europium chelate on the **HVEM** receptor to an allophycocyanin (APC) acceptor on the ligand, Specific time resolved emission from the acceptor is observed on receptor:ligand complex formation, The results of various direct and indirect labeling strategies are described. Several assay optimization experiments were necessary to obtain an assay that was robust to automation and file compound interference while sensitive to the effect of potential inhibitors. The signal was stable for more than 24 h at room temperature using the Eu3+ chelates, suggesting no dissociation of the lanthanide ion. The 384-well assay was readily automated and was able to identify more than 99.5% of known positive controls in the validation studies successfully. Screening identified both a series of known potent inhibitors and several structural classes of hits that readily deconvoluted to yield single compound inhibitors with the desired functional activity in secondary biological assays. The equivalence of the data in 384- and 1536-well formats indicates that routine implementation of 1536-well chelate-based energy transfer screening appears to be primarily limited by liquid handling rather than detection issues.

L3 ANSWER 19 OF 39 CAPLUS COPYRIGHT 2002 ACS
1998:405987 Document No. 129:94450 **Herpesvirus entry mediator** (**HVEM**) polypeptides and uses thereof.
Ashkenazi, Avi J.; Marsters, Scot A. (Genentech, Inc., USA). PCT Int. Appl. WO 9825967 A1 19980618, 46 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US22278 19971205. PRIORITY: US 1996-32705 19961212.

AB Novel polypeptides, designated **HVEM**, are provided. Compns. including **HVEM** chimeras, nucleic acid encoding **HVEM**, and antibodies to **HVEM** are also provided. Also claimed were non-human transgenic animal or knockout mice or rats that expressing **HVEM** polypeptide or altered **HVEM** gene and polypeptide. The **HVEM** protein, gene, antibody, chimeras, are transgenic animal are useful in understanding **HVEM** protein in pathol. condition and in therapy and nontherapy applications. The nucleic acid sequence and amino acid sequence of **HVEM** were detd. and are similar to human tumor necrosis factor receptor family.

L3 ANSWER 20 OF 39 MEDLINE DUPLICATE 7
1998438532 Document Number: 98438532. PubMed ID: 9765287.
Herpesvirus entry mediator ligand (**HVEM**-L), a novel ligand for **HVEM**/TR2, stimulates proliferation of T cells and inhibits HT29 cell growth. Harrop J A;

McDonnell P C; Brigham-Burke M; Lyn S D; Minton J; Tan K B; Dede K; Spampanato J; Silverman C; Hensley P; DiPrinzio R; Emery J G; Deen K; Eichman C; Chabot-Fletcher M; Truneh A; Young P R. (Department of Molecular and Cellular Immunology, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania 19406, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Oct 16) 273 (42) 27548-56. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB **Herpesvirus entry mediator** (**HVEM**), a member of the tumor necrosis factor (TNF) receptor family, mediates herpesvirus entry into cells during infection. Upon overexpression, **HVEM** activates NF-kappaB and AP-1 through a TNF receptor-associated factor (TRAF)-mediated mechanism. Using an **HVEM**-Fc fusion protein, we screened soluble forms of novel TNF-related proteins derived from an expressed sequence tag data base. One of these, which we designated **HVEM**-L, specifically bound to **HVEM**-Fc with an affinity of 44 nM. This association was confirmed with soluble and membrane forms of both receptor and ligand. **HVEM** -L mRNA is expressed in spleen, lymph nodes, macrophages, and T cells and encodes a 240-amino acid protein. A soluble, secreted form of the protein stimulates proliferation of T lymphocytes during allogeneic responses, inhibits HT-29 cell growth, and weakly stimulates NF-kappaB-dependent transcription.

L3 ANSWER 21 OF 39 MEDLINE DUPLICATE 8

1998362108 Document Number: 98362108. PubMed ID: 9696799. Herpes simplex virus glycoprotein D can bind to poliovirus receptor-related protein 1 or **herpesvirus entry mediator**, two structurally unrelated mediators of virus entry. Krummenacher C; Nicola A V; Whitbeck J C; Lou H; Hou W; Lambris J D; Geraghty R J; Spear P G; Cohen G H; Eisenberg R J. (Department of Microbiology, School of Dental Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.. krumm@biochem.dental.upenn.edu) . JOURNAL OF VIROLOGY, (1998 Sep) 72 (9) 7064-74. Journal code: KCV; 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Several cell membrane proteins have been identified as herpes simplex virus (HSV) entry mediators (Hve). HveA (formerly **HVEM**) is a member of the tumor necrosis factor receptor family, whereas the poliovirus receptor-related proteins 1 and 2 (PRR1 and PRR2, renamed HveC and HveB) belong to the immunoglobulin superfamily. Here we show that a truncated form of HveC directly binds to HSV glycoprotein D (gD) in solution and at the surface of virions. This interaction is dependent on the native conformation of gD but independent of its N-linked glycosylation. Complex formation between soluble gD and HveC appears to involve one or two gD molecules for one HveC protein. Since HveA also mediates HSV entry by interacting with gD, we compared both structurally unrelated receptors for their binding to gD. Analyses of several gD variants indicated that structure and accessibility of the N-terminal domain of gD, essential for HveA binding, was not necessary for HveC interaction. Mutations in functional regions II, III, and IV of gD had similar effects on binding to either HveC or HveA. Competition assays with neutralizing anti-gD monoclonal antibodies (MAbs) showed that MAbs from group Ib prevented HveC and HveA binding to virions. However, group Ia MAbs blocked HveC but not HveA binding, and conversely, group VII MAbs blocked HveA but not HveC binding. Thus, we propose that HSV entry can be mediated by two structurally unrelated gD receptors through related but not identical binding with gD.

L3 ANSWER 22 OF 39 MEDLINE DUPLICATE 9

1998285738 Document Number: 98285738. PubMed ID: 9621040. HveA (**herpesvirus entry mediator** A), a coreceptor for herpes simplex virus entry, also participates in virus-induced cell fusion. Terry-Allison T; Montgomery R I; Whitbeck J C; Xu R; Cohen G H; Eisenberg R J; Spear P G. (Department of Microbiology-Immunology, Northwestern University Medical School, Chicago, Illinois 60611, USA.) JOURNAL OF VIROLOGY, (1998 Jul) 72 (7) 5802-10. Journal code: KCV;

0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The purpose of this study was to determine whether a cell surface protein that can serve as coreceptor for herpes simplex virus type 1 (HSV-1) entry, **herpesvirus entry mediator** (previously designated **HVEM** but renamed HveA), also mediates HSV-1-induced cell-cell fusion. We found that transfection of DNA from KOS-804, a previously described HSV-1 syncytial (Syn) strain whose Syn mutation was mapped to an amino acid substitution in gK, induced numerous large syncytia on HveA-expressing Chinese hamster ovary cells (CHO-HVEM12) but not on control cells (CHO-C8). Antibodies specific for gD as well as for HveA were effective inhibitors of KOS-804-induced fusion, consistent with previously described direct interactions between gD and HveA. Since mutations in gD determine the ability of HSV-1 to utilize HveA for entry, we examined whether the form of virally expressed gD also influenced the ability of HveA to mediate fusion. We produced a recombinant virus carrying the KOS-804 Syn mutation and the KOS-Rid1 gD mutation, which significantly reduces viral entry via HveA, and designated it KOS-SR1. KOS-SR1 DNA had a markedly reduced ability to induce syncytia on CHO-HVEM12 cells and a somewhat enhanced ability to induce syncytia on CHO-C8 cells. These results support previous findings concerning the relative abilities of KOS and KOS-Rid1 to infect CHO-HVEM12 and CHO-C8 cells. Thus, HveA mediates cell-cell fusion as well as viral entry and both activities of HveA are contingent upon the form of gD expressed by the virus.

L3 ANSWER 23 OF 39 MEDLINE DUPLICATE 10

1998216718 Document Number: 98216718. PubMed ID: 9557640. Monoclonal antibodies to distinct sites on herpes simplex virus (HSV) glycoprotein D block HSV binding to **HVEM**. Nicola A V; Ponce de Leon M; Xu R; Hou W; Whitbeck J C; Krummenacher C; Montgomery R I; Spear P G; Eisenberg R J; Cohen G H. (Department of Microbiology, School of Dental Medicine, University of Pennsylvania, Philadelphia 19104-6002, USA.) JOURNAL OF VIROLOGY, (1998 May) 72 (5) 3595-601. Journal code: KCV; 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **HVEM** (for **herpesvirus entry mediator**) is a member of the tumor necrosis factor receptor superfamily and mediates entry of many strains of herpes simplex virus (HSV) into normally nonpermissive Chinese hamster ovary (CHO) cells. We used sucrose density centrifugation to demonstrate that purified HSV-1 KOS virions bind directly to a soluble, truncated form of **HVEM** (HVEMt) in the absence of any other cell-associated components. Therefore, **HVEM** mediates HSV entry by serving as a receptor for the virus. We previously showed that soluble, truncated forms of HSV glycoprotein D (gDt) bind to HVEMt in vitro. Here we show that antibodies specific for gD, but not the other entry glycoproteins gB, gC, or the gH/gL complex, completely block HSV binding to **HVEM**. Thus, virion gD is the principal mediator of HSV binding to **HVEM**. To map sites on virion gD which are necessary for its interaction with **HVEM**, we preincubated virions with gD-specific monoclonal antibodies (MAbs). MAbs that recognize antigenic sites Ib and VII of gD were the only MAbs which blocked the HSV-**HVEM** interaction. MAbs from these two groups failed to coprecipitate HVEMt in the presence of soluble gDt, whereas the other anti-gD MAbs coprecipitated HVEMt and gDt. Previous mapping data indicated that site VII includes amino acids 11 to 19 and site Ib includes 222 to 252. The current experiments indicate that these sites contain residues important for HSV binding to **HVEM**. Group Ib and VII MAbs also blocked HSV entry into **HVEM**-expressing CHO cells. These results suggest that the mechanism of neutralization by these MAbs is via interference with the interaction between gD in the virus and **HVEM** on the cell. Group Ia and II MAbs failed to block HSV binding to **HVEM** yet still neutralized **HVEM**-mediated entry, suggesting that these MAbs block entry at a step other than **HVEM** binding.

L3 ANSWER 24 OF 39 SCISEARCH COPYRIGHT 2002 ISI (R)

1998:762711 The Genuine Article (R) Number: 121HC. LIGHT, a new pro-apoptotic cytokine member of the TNF superfamily, and lymphotoxin-alpha are ligands for the **herpesvirus entry mediator** (**HVEM**).. Mauri D (Reprint); Ebner R; Montgomery R; Kochel K; Cheung T C; Yu G L; Ruben S; Murphy M; Eisenberg R J; Cohen G H; Spear P G; Ware C F. LA JOLLA INST ALLERGY & IMMUNOL, SAN DIEGO, CA 92121; HUMAN GENOME SCI INC, ROCKVILLE, MD 20850; NORTHWESTERN UNIV, CHICAGO, IL 60611; UNIV PENN, PHILADELPHIA, PA 19104. FASEB JOURNAL (17 MAR 1998) Vol. 12, No. 4, Part 1, Supp. [S], pp. 1754-1754. Publisher: FEDERATION AMER SOC EXP BIOL. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998. ISSN: 0892-6638. Pub. country: USA. Language: English.

L3 ANSWER 25 OF 39 MEDLINE DUPLICATE 11
1998105787 Document Number: 98105787. PubMed ID: 9445042.
Herpesvirus entry mediator HVEM mediates cell-cell spread in BHK(TK-) cell clones. Roller R J; Rauch D. (Department of Microbiology, University of Iowa, Iowa City 52242, USA.. richardroller@uiowa.edu) . JOURNAL OF VIROLOGY, (1998 Feb) 72 (2) 1411-7. Journal code: KCV; 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.
AB 95-19 and U(S)11c119.3 are BHK(TK-)-derived cell lines that are highly resistant to postattachment entry of herpes simplex virus type 1 (HSV-1) and HSV-2 but not to later steps in single-step replication. The resistance properties of these two cell types are not identical. U(S)11c119.3 cells are fully susceptible to pseudorabies virus (PRV), as shown by single-step growth experiments, whereas 95-19 cells are resistant to entry of free PRV but not to entry by cell-cell spread. We have tested the ability of **HVEM** to overcome the block to infection in both cell lines following transient and stable transfection. **HVEM** was able to mediate entry of free HSV-1 into both cell lines, as shown by an increase in the number of beta-galactosidase-expressing cells in cultures transiently transfected with an **HVEM** expression plasmid and infected with lacZ-expressing HSV-1. In stably transfected 95-19 cells, **HVEM** enhanced infection by free HSV-1, as shown by an increase in the number of infectious centers obtained following infection. In both cell types, **HVEM** strongly enhanced entry of HSV-1 and HSV-2 by cell-cell spread, suggesting that **HVEM** can function as an entry mediator both in entry of free virus and in entry by cell-cell spread.

L3 ANSWER 26 OF 39 MEDLINE
1998411370 Document Number: 98411370. PubMed ID: 9739048. LIGHT, a novel ligand for lymphotoxin beta receptor and TR2/**HVEM** induces apoptosis and suppresses in vivo tumor formation via gene transfer. Zhai Y; Guo R; Hsu T L; Yu G L; Ni J; Kwon B S; Jiang G W; Lu J; Tan J; Ugustus M; Carter K; Rojas L; Zhu F; Lincoln C; Endress G; Xing L; Wang S; Oh K O; Gentz R; Ruben S; Lippman M E; Hsieh S L; Yang D. (Human Genome Sciences, Inc., Rockville, Maryland 20850, USA.) JOURNAL OF CLINICAL INVESTIGATION, (1998 Sep 15) 102 (6) 1142-51. Journal code: HS7; 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.
AB LIGHT is a new member of tumor necrosis factor (TNF) cytokine family derived from an activated T cell cDNA library. LIGHT mRNA is highly expressed in splenocytes, activated PBL, CD8(+) tumor infiltrating lymphocytes, granulocytes, and monocytes but not in the thymus and the tumor cells examined. Introduction of LIGHT cDNA into MDA-MB-231 human breast carcinoma caused complete tumor suppression in vivo. Histological examination showed marked neutrophil infiltration and necrosis in LIGHT expressing but not in the parental or the Neo-transfected MDA-MB-231 tumors. Interferon gamma (IFNgamma) dramatically enhances LIGHT-mediated apoptosis. LIGHT protein triggers apoptosis of various tumor cells expressing both lymphotoxin beta receptor (LTbetaR) and TR2/**HVEM** receptors, and its cytotoxicity can be blocked specifically by addition of a LTbetaR-Fc or a TR2/**HVEM**-Fc fusion protein. However, LIGHT was not cytolytic to the tumor cells that express only the LTbetaR or the TR2/**HVEM** or hematopoietic cells examined that express only the TR2/**HVEM**, such as PBL, Jurkat cells, or CD8(+) TIL cells. In contrast,

treatment of the activated PBL with LIGHT resulted in release of IFNgamma. Our data suggest that LIGHT triggers distinct biological responses based on the expression patterns of its receptors on the target cells. Thus, LIGHT may play a role in the immune modulation and have a potential value in cancer therapy.

L3 ANSWER 27 OF 39 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1998:200127 Document No.: PREV199800200127. Light, a new pro-apoptotic cytokine member of the TNF superfamily, and lymphotoxin-alpha are ligands for the **herpesvirus entry mediator** (**HVEM**. Mauri, D. (1); Ebner, R.; Montgomery, R.; Kochel, K. (1); Cheung, T. C. (1); Yu, G.-L.; Ruben, S.; Murphy, M.; Eisenberg, R. J.; Cohen, G. H.; Spear, P. G.; Ware, C. F. (1). (1) La Jolla Inst. Allergy and Immunol., San Diego, CA 92121 USA. FASEB Journal, (March 17, 1998) Vol. 12, No. 4, pp. A301. Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology 98, Part 1 San Francisco, California, USA April 18-22, 1998 Federation of American Societies for Experimental Biology. ISSN: 0892-6638. Language: English.

L3 ANSWER 28 OF 39 SCISEARCH COPYRIGHT 2002 ISI (R)
1998:891021 The Genuine Article (R) Number: 136CD. Light, a new lymphotoxin-related cytokine that engages the LT beta receptor and **herpesvirus entry mediator** (**HVEM**). Ware C F (Reprint); Butrovich K D; Mauri D N; Tillman J; Rooney I. LA JOLLA INST ALLERGY & IMMUNOL, SAN DIEGO, CA 92121. EUROPEAN CYTOKINE NETWORK (SEP 1998) Vol. 9, No. 3, pp. 285-285. Publisher: JOHN LIBBEY EUROTEXT LTD. 127 AVE DE LA REPUBLIQUE, 92120 MONTROUGE, FRANCE. ISSN: 1148-5493. Pub. country: USA. Language: English.

L3 ANSWER 29 OF 39 MEDLINE DUPLICATE 12
1998321161 Document Number: 98321161. PubMed ID: 9657005. A cell surface protein with herpesvirus entry activity (HveB) confers susceptibility to infection by mutants of herpes simplex virus type 1, herpes simplex virus type 2, and pseudorabies virus. Warner M S; Geraghty R J; Martinez W M; Montgomery R I; Whitbeck J C; Xu R; Eisenberg R J; Cohen G H; Spear P G. (Department of Microbiology-Immunology, Northwestern University Medical School, Chicago, Illinois 60611, USA.) VIROLOGY, (1998 Jun 20) 246 (1) 179-89. Journal code: XEA; 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.
AB Certain mutant strains of herpes simplex virus type 1 (HSV-1) are unable to infect cells in which entry is dependent on **HVEM**, the previously described **herpesvirus entry mediator** designated here as herpesvirus entry protein A (HveA). These mutant viruses can infect other cells where entry is apparently dependent on other co-receptors. The mutant virus HSV-1(KOS)Rid1 was used to screen a human cDNA expression library for ability of transfected plasmids to convert resistant Chinese hamster ovary cells to susceptibility to virus entry. A plasmid expressing the previously described poliovirus receptor-related protein 2 (Prr2) was isolated on the basis of this activity. This protein, designated here as HveB, was shown to mediate the entry of three mutant HSV-1 strains that cannot use **HVEM** as co-receptor, but not wild-type HSV-1 strains. HveB also mediated the entry of HSV-2 and pseudorabies virus but not bovine herpesvirus type 1. HveB was expressed in some human neuronal cell lines, fibroblastic cells, keratinocytes, and primary activated T lymphocytes. Antibodies specific for HveB blocked infection of HveB-expressing CHO cells and a human fibroblastic cell strain HEL299. Differences in ability of HSV-1 and HSV-2 strains to use HveB for entry should influence the types of cells that can be infected and thereby account in part for serotype and strain differences in tissue tropism and pathogenicity.

L3 ANSWER 30 OF 39 MEDLINE DUPLICATE 13
1998442215 Document Number: 98442215. PubMed ID: 9770079. The role of herpes simplex virus glycoproteins in the virus replication cycle. Rajcani J; Vojvodova A. (Institute of Virology, Slovak Academy of Sciences,

Massachusetts, USA May 17-21, 1998 ISSN: 1079-9907. Language: English.

L3 ANSWER 34 OF 39 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1998:458017 Document No.: PREV199800458017. Lymphotoxins meet herpesvirus: New light on the darkside of virus-host interactions. Ware, C. F. (1); Mauri, D. M. (1); Ebner, R.; Montgomery, R. I.; Kochel, K. D. (1); Cheung, T. C. (1); Yu, G.-L.; Ruben, S.; Murphy, M.; Eisenberg, R. J.; Cohen, G. H.; Spear, P. G.. (1) La Jolla Inst. Allergy Immunol., San Diego, CA 92121 USA. Journal of Interferon and Cytokine Research, (May, 1998) Vol. 18, No. 5, pp. A36. Meeting Info.: 7th International Conference on Tumor Necrosis Factor and Related Molecules Scientific Advances and Medical Applications Hyannis, Massachusetts, USA May 17-21, 1998 ISSN: 1079-9907. Language: English.

L3 ANSWER 35 OF 39 MEDLINE DUPLICATE 14
1998122340 Document Number: 98122340. PubMed ID: 9462508. LIGHT, a new member of the TNF superfamily, and lymphotoxin alpha are ligands for **herpesvirus entry mediator**. Mauri D N; Ebner R; Montgomery R I; Kochel K D; Cheung T C; Yu G L; Ruben S; Murphy M; Eisenberg R J; Cohen G H; Spear P G; Ware C F. (Division of Molecular Immunology, La Jolla Institute for Allergy and Immunology, San Diego, California 92121, USA.) IMMUNITY, (1998 Jan) 8 (1) 21-30. Journal code: CCF; 9432918. ISSN: 1074-7613. Pub. country: United States. Language: English.
AB Herpes simplex virus (HSV) 1 and 2 infect activated T lymphocytes by attachment of the HSV envelope glycoprotein D (gD) to the cellular **herpesvirus entry mediator** (**HVEM**), an orphan member of the tumor necrosis factor receptor superfamily. Here, we demonstrate that **HVEM** binds two cellular ligands, secreted lymphotoxin alpha (LTalpha) and LIGHT, a new member of the TNF superfamily. LIGHT is a 29 kDa type II transmembrane protein produced by activated T cells that also engages the receptor for the LTalphabeta heterotrimer but does not form complexes with either LTalpha or LTbeta. HSV1 gD inhibits the interaction of **HVEM** with LIGHT, and LIGHT and gD interfere with **HVEM**-dependent cell entry by HSV1. This characterizes herpesvirus gD as a membrane-bound viokine and establishes LIGHT-**HVEM** as integral components of the lymphotoxin cytokine-receptor system.

L3 ANSWER 36 OF 39 MEDLINE DUPLICATE 15
97306297 Document Number: 97306297. PubMed ID: 9162022. **Herpesvirus entry mediator**, a member of the tumor necrosis factor receptor (TNFR) family, interacts with members of the TNFR-associated factor family and activates the transcription factors NF-kappaB and AP-1. Marsters S A; Ayres T M; Skubatch M; Gray C L; Rothe M; Ashkenazi A. (Department of Molecular Oncology, Genentech, Inc., South San Francisco, California 94080-4918, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 May 30) 272 (22) 14029-32. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB The mammalian tumor necrosis factor receptor (TNFR) family consists of 10 cell-surface proteins that regulate development and homeostasis of the immune system. Based on an expressed sequence tag, we have cloned a cDNA encoding a novel member of the human TNFR family. A closely related protein, designated **HVEM** (for **herpesvirus entry mediator**), was identified independently by another group as a mediator of herpesvirus entry into mammalian cells (Montgomery, R., Warner, M., Lum, B., and Spear, P. (1996) Cell 87, 427-436). **HVEM** differed from our clone by two amino acid residues, suggesting that the two proteins represent polymorphism of a single **HVEM** gene. We detected **HVEM** mRNA expression in several human fetal and adult tissues, although the predominant sites of expression were lymphocyte-rich tissues such as adult spleen and peripheral blood leukocytes. The cytoplasmic region of **HVEM** bound to several members of the TNFR-associated factor (TRAF) family, namely TRAF1, TRAF2, TRAF3, and TRAF5, but not to TRAF6. Transient

transfection of **HVEM** into human 293 cells caused marked activation of nuclear factor-kappaB (NF-kappaB), a transcriptional regulator of multiple immunomodulatory and inflammatory genes. **HVEM** transfection induced also marked activation of Jun N-terminal kinase, and of the Jun-containing transcription factor AP-1, a regulator of cellular stress-response genes. These results suggest that **HVEM** is linked via TRAFs to signal transduction pathways that activate the immune response.

L3 ANSWER 37 OF 39 MEDLINE DUPLICATE 16

97366672 Document Number: 97366672. PubMed ID: 9223502. Glycoprotein D of herpes simplex virus (HSV) binds directly to **HVEM**, a member of the tumor necrosis factor receptor superfamily and a mediator of HSV entry. Whitbeck J C; Peng C; Lou H; Xu R; Willis S H; Ponce de Leon M; Peng T; Nicola A V; Montgomery R I; Warner M S; Soulika A M; Spruce L A; Moore W T; Lambris J D; Spear P G; Cohen G H; Eisenberg R J. (School of Dental Medicine, Center for Oral Health Research, University of Pennsylvania, Philadelphia 19104, USA.) JOURNAL OF VIROLOGY, (1997 Aug) 71 (8) 6083-93. Journal code: KCV; 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Glycoprotein D (gD) is a structural component of the herpes simplex virus (HSV) envelope which is essential for virus entry into host cells. Chinese hamster ovary (CHO-K1) cells are one of the few cell types which are nonpermissive for the entry of many HSV strains. However, when these cells are transformed with the gene for the **herpesvirus entry mediator** (**HVEM**), the resulting cells, CHO-HVEM12, are permissive for many HSV strains, such as HSV-1(KOS). By virtue of its four cysteine-rich pseudorepeats, **HVEM** is a member of the tumor necrosis factor receptor superfamily of proteins. Recombinant forms of gD and **HVEM**, gD-1(306t) and **HVEM**(200t), respectively, were used to demonstrate a specific physical interaction between these two proteins. This interaction was dependent on native gD conformation but independent of its N-linked oligosaccharides, as expected from previous structure-function studies. Recombinant forms of gD derived from HSV-1(KOS)rid1 and HSV-1(ANG) did not bind to **HVEM**(200t), explaining the inability of these viruses to infect CHO-HVEM12 cells. A variant gD protein, gD-1(delta290-299t), showed enhanced binding to **HVEM**(200t) relative to the binding of gD-1(306t). Competition studies showed that gD-1(delta290-299t) and gD-1(306t) bound to the same region of **HVEM**(200t), suggesting that the differences in binding to **HVEM** are due to differences in affinity. These differences were also reflected in the ability of gD-1(delta290-299t) but not gD-1(306t) to block HSV type 1 infection of CHO-HVEM12 cells. By gel filtration chromatography, the complex between gD-1(delta290-299t) and **HVEM**(200t) had a molecular mass of 113 kDa and a molar ratio of 1:2. We conclude that **HVEM** interacts directly with gD, suggesting that **HVEM** is a receptor for virion gD and that the interaction between these proteins is a step in HSV entry into **HVEM**-expressing cells.

L3 ANSWER 38 OF 39 CAPLUS COPYRIGHT 2002 ACS

1998:29120 Document No. 128:165342 Characterization of a novel TNF-like ligand and recently described TNF ligand and TNF receptor superfamily genes and their constitutive and inducible expression in hematopoietic and non-hematopoietic cells. Tan, K. B.; Harrop, Jeremy; Reddy, Manjula; Young, Peter; Terrett, Jonathan; Emery, John; Moore, Gordon; Truneh, Alemseged (Department Molecular Immunology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406-0939, USA). Gene, 204(1/2), 35-46 (English) 1997. CODEN: GENED6. ISSN: 0378-1119. Publisher: Elsevier Science B.V..

AB A novel (TL1), a recently described (TL2) TNF-like, and three recently described TNF receptor-like (TR1, TR2, TR3) mols. were identified by searching a cDNA database. TL1 and TL2 are type-II membrane proteins. TR2 and TR3 and type-I membrane proteins whereas TR1 appears to be a secreted protein. TL1, TL2, TR2 and TR3 were expressed in hematopoietic

cells, whereas TR1 was not. Northern blots hybridized with the cDNA probes revealed multiple forms of RNA as well as inducible expression of TL1, TL2, TR2 and TR3. TL2 and TR3, in particular, were highly induced in activated CD4+ T cells. Radiation hybrid mapping localized TR1 and TL2 to 8q24 and 3q26, resp., which are not near any known superfamily members. TL1 was mapped to 9q32, near CD30L (9q33) and TR2 and TR3 mapped to the region of chromosome 1 that contains the TNFR-II, 4-1BB, OX40 and CD30 gene cluster at 1p36. Only TR3 in this cluster possesses a death domain. Southern blot anal. revealed the presence of TL and TR genes in different mammalian species. TL2, TR1, TR2 and TR3 were recently described by others as TRAIL/Apo-2L, OPG, **HVEM** and DR3/WSL-1/Apo-3/TRAMP/LARD, resp.

L3 ANSWER 39 OF 39 MEDLINE DUPLICATE 17
97053782 Document Number: 97053782. PubMed ID: 8898196. Herpes simplex virus-1 entry into cells mediated by a novel member of the TNF/NGF receptor family. Montgomery R I; Warner M S; Lum B J; Spear P G. (Northwestern University Medical School, Department of Microbiology-Immunology, Chicago, Illinois 60611, USA.) CELL, (1996 Nov 1) 87 (3) 427-36. Journal code: CQ4; 0413066. ISSN: 0092-8674. Pub. country: United States. Language: English.

AB We identified and cloned a cellular mediator of herpes simplex virus (HSV) entry. Hamster and swine cells resistant to viral entry became susceptible upon expression of a human cDNA encoding this protein, designated **HVEM** (for **herpesvirus entry mediator**). **HVEM** was shown to mediate the entry of several wild-type HSV strains of both serotypes. Anti-**HVEM** antibodies and a soluble hybrid protein containing the **HVEM** ectodomain inhibited **HVEM**-dependent infection but not virus binding to cells. Mutations in the HSV envelope glycoprotein gD significantly reduced **HVEM** -mediated entry. The contribution of **HVEM** to HSV entry into human cells was demonstrable in activated T cells. **HVEM**, the first identified mediator of HSV entry, is a new member of the TNF/NGF receptor family.

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 08:16:51 ON 26 FEB 2002

L1 237 S HERPESVIRUS ENTRY MEDIATOR
L2 96 S L1 AND "HVEM"
L3 39 DUP REMOVE L2 (57 DUPLICATES REMOVED)
L4 0 S L3 AND INHIBIT PROLIFERATION

=> s l2 and ligand
L5 40 L2 AND LIGAND

=> dup remove l5
PROCESSING COMPLETED FOR L5
L6 22 DUP REMOVE L5 (18 DUPLICATES REMOVED)

=> d l6 1-22 cbib abs

L6 ANSWER 1 OF 22 MEDLINE DUPLICATE 1
2002111908 Document Number: 21826705. PubMed ID: 11836420. Effects of herpes simplex virus on structure and function of nectin-1/HveC. Krummenacher Claude; Baribaud Isabelle; Sanzo James F; Cohen Gary H; Eisenberg Roselyn J. (Department of Microbiology, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA.. krumm@biochem.dental.upenn.edu) . JOURNAL OF VIROLOGY, (2002 Mar) 76 (5) 2424-33. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Herpes simplex virus (HSV) entry requires the interaction between the envelope glycoprotein D (gD) and a cellular receptor such as nectin-1 (also named **herpesvirus entry mediator** C [HveC]) or HveA/**HVEM**. Nectin-1 is a cell adhesion molecule found at adherens junctions associated with the cytoplasmic actin-binding protein afadin. Nectin-1 can act as its own **ligand** in a homotypic interaction to bridge cells together. We used a cell aggregation assay to map an adhesive functional site on nectin-1 and identify the effects of gD binding and HSV early infection on nectin-1 function. Soluble forms of nectin-1 and anti-nectin-1 monoclonal antibodies were used to map a functional adhesive site within the first immunoglobulin-like domain (V domain) of nectin-1. This domain also contains the gD-binding site, which appeared to overlap the adhesive site. Thus, soluble forms of gD were able to prevent nectin-1-mediated cell aggregation and to disrupt cell clumps in an affinity-dependent manner. HSV also prevented nectin-1-mediated cell aggregation by occupying the receptor. Early in infection, nectin-1 was not downregulated from the cell surface. Rather, detection of nectin-1 changed gradually over a 30-min period of infection, as reflected by a decrease in the CK41 epitope and an increase in the CK35 epitope. The level of detection of virion gD on the cell surface increased within 5 min of infection in a receptor-dependent manner. These observations suggest that cell surface nectin-1 and gD may undergo conformational changes during HSV entry as part of an evolving interaction between the viral envelope and the cell plasma membrane.

L6 ANSWER 2 OF 22 MEDLINE DUPLICATE 2
2002045584 Document Number: 21629477. PubMed ID: 11756979. Search for polymorphisms in the genes for **herpesvirus entry mediator**, nectin-1, and nectin-2 in immune seronegative individuals. Struyf Frank; Posavad Christine M; Keyaerts Els; Van Ranst Marc; Corey Lawrence; Spear Patricia G. (Department of Microbiology-Immunology, Northwestern University Medical School, Chicago, Illinois 60611, USA.) JOURNAL OF INFECTIOUS DISEASES, (2002 Jan 1) 185 (1) 36-44. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Recently, individuals have been identified who possess T cell responses to herpes simplex virus (HSV) antigens despite the absence of detectable anti-HSV antibodies in their serum. The significance of this immune seronegative status is unclear, but it could indicate resistance to overt HSV infection. The aims of the present study were to investigate whether genetic differences in receptors used by HSV for cell entry (**herpesvirus entry mediator** [**HVEM**], nectin-1, and nectin-2) could be detected in immune seronegative individuals. Coding polymorphisms were identified in the **HVEM** and nectin-1 genes. The variant receptor proteins were expressed, and their ability to bind the viral **ligand** glycoprotein D and to mediate HSV entry after transient transfection into normally resistant cells was compared with that of their wild-type counterparts. HSV entry activity in wild-type and variant forms of the receptors was indistinguishable, which indicates that the polymorphisms observed are unlikely to explain the possible restrictions on HSV replication or spread in immune seronegative individuals.

L6 ANSWER 3 OF 22 CAPLUS COPYRIGHT 2002 ACS
2001:598037 Document No. 135:179726 Identification of a novel domain in the tumor necrosis factor receptor family that mediates pre-**ligand** receptor assembly and function. Lenardo, Michael J.; Chan, Francis Ka-ming; Siegel, Richard M. (Government of the United States of America as Represented by the Secretary, Department of Health and Human Services, USA). PCT Int. Appl. WO 2001058953 A2 20010816, 77 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,

MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US4125 20010209. PRIORITY: US 2000-PV181909 20000211.

AB The authors disclose the identification and characterization of an amino acid sequence termed PLAD (pre-**ligand** assembly domain) found in the extracellular domains of the TNF receptor superfamily. In one example, self-assocn. of the p60 and p80 receptor monomers was demonstrated to occur in the absence of the TNF-.alpha. **ligand**. In a second example using wild-type and engineered constructs of CD95, the apoptotic signaling function was shown to correlate with the ability to self-assoc. independent of **ligand** binding.

L6 ANSWER 4 OF 22 CAPLUS COPYRIGHT 2002 ACS

2001:354356 Document No. 135:120439 Alterations of gene expression during colorectal carcinogenesis revealed by cDNA microarrays after laser-capture microdissection of tumor tissues and normal epithelia. Kitahara, Osamu; Furukawa, Yoichi; Tanaka, Toshihiro; Kihara, Chikashi; Ono, Kenji; Yanagawa, Renpei; Nita, Marcelo E.; Takagi, Toshihisa; Nakamura, Yusuke; Tsunoda, Tatsuhiko (Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo, 108-8639, Japan). Cancer Research, 61(9), 3544-3549 (English) 2001. CODEN: CNREA8. ISSN: 0008-5472. Publisher: American Association for Cancer Research.

AB To identify a set of genes involved in the development of colorectal carcinogenesis, we compared expression profiles of colorectal cancer cells from eight tumors with corresponding noncancerous colonic epithelia using a DNA microarray consisting of 9216 human genes. These cell populations had been rendered homogeneous by laser-capture microdissection. Expression change in more than half of the tumors was obsd. for 235 genes, i.e., 44 up-regulated and 191 down-regulated genes. The differentially expressed genes include those assocd. with signal transduction, metabolizing enzymes, prodn. of reactive oxygen species, cell cycle, transcription, mitosis, and apoptosis. Subsequent examn. of 10 genes (five up-regulated and five down-regulated) by semiquant. reverse transcription-PCR using the eight tumors together with an addnl. 12 samples substantiated the reliability of our anal. The extensive list of genes identified in these expts. provides a large body of potentially valuable information of colorectal carcinogenesis and represents a source of novel targets for cancer therapy.

L6 ANSWER 5 OF 22 MEDLINE DUPLICATE 3

2001680220 Document Number: 21583213. PubMed ID: 11726199. LIGHT, a member of the TNF superfamily, induces morphological changes and delays proliferation in the human rhabdomyosarcoma cell line RD. Hikichi Y; Matsui H; Tsuji I; Nishi K; Yamada T; Shintani Y; Onda H. (Discovery Research Laboratories I, Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 10 Wadai, Tsukuba, Ibaraki 300-4293, Japan.) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2001 Dec 7) 289 (3) 670-7. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB LIGHT is a member of the tumor necrosis factor (TNF) superfamily, which binds two known receptors, lymphotoxin-beta receptor (LTbetaR) and the **herpesvirus entry mediator (HVEM**)/TR2. We investigated the effects of LIGHT on the human rhabdmyosarcoma cell line RD. LIGHT delayed cell proliferation and induced morphological changes of the cells. These effects were not shown by other TNF family **ligands** such as TNFalpha and LTalpha, which induced the transcriptional activity of nuclear factor-kappaB (NF-kappaB) and NF-kappaB-responsible chemokine productions in the same manner as did LIGHT. LTalpha1beta2, another TNF family **ligand** for LTbetaR, was shown to have similar activities in RD cells as LIGHT. Both LIGHT and LTalpha1beta2 induced the expression of muscle-specific genes such as smooth muscle (SM) alpha-actin, while TNFalpha and LTalpha did not. These findings indicate that LIGHT may be a novel inducer of RD cell differentiation associated with SM alpha-actin expression through the

LTbetaR.
(c) 2001 Elsevier Science.

L6 ANSWER 6 OF 22 MEDLINE DUPLICATE 4
2001371428 Document Number: 21322536. PubMed ID: 11429164. Recombinant, soluble LIGHT (**HVEM ligand**) induces increased IL-8 secretion and growth arrest in A375 melanoma cells. Hehlgans T; Mannel D N. (Institute of Pathology/Tumor Immunology, University of Regensburg, F.-J.-Strauss-Allee 11, D-93042 Regensburg, Germany.) JOURNAL OF INTERFERON AND CYTOKINE RESEARCH, (2001 May) 21 (5) 333-8. Journal code: CD4; 9507088. ISSN: 1079-9907. Pub. country: United States. Language: English.

AB The heterotrimeric lymphotoxin alpha(1)beta(2) (LTalpha(1)beta(2)) complex and LIGHT, a new member of the tumor necrosis factor (TNF) superfamily, have been identified as membrane-anchored **ligands** for the LTbeta receptor (LTbetaR), a member of the TNF receptor (TNFR) superfamily. Although some of the biologic activities of this receptor have been described using either soluble LTalpha(1)beta(2) as a **ligand** or agonistic monoclonal antibodies (mAb), very little is known about the signaling of LIGHT via the LTbetaR. To gain more insight into the biologic functions of LIGHT, we generated a recombinant soluble form of human LIGHT (rsHuLIGHT). We demonstrate here that this rsHuLIGHT is capable of binding to the LTbetaR. Interestingly, receptor-mediated **ligand** precipitation analysis revealed that rsHuLIGHT bound only to human LTbetaR but not to mouse LTbetaR, indicating a species-specific receptor **ligand** interaction. Activation of A375 human melanoma cells by rsHuLIGHT induced an increased secretion of interleukin-8 (IL-8). Furthermore, rsHuLIGHT caused growth arrest of A375 cells even in the absence of interferon-gamma (IFN-gamma).

L6 ANSWER 7 OF 22 CAPLUS COPYRIGHT 2002 ACS
2000:421293 Document No. 133:57683 A method of manufacturing active lymphotoxin-.beta. receptor immunoglobulin chimeric proteins. Browning, Jeffrey; Miatkowski, Konrad; Meier, Werner (Biogen, Inc., USA). PCT Int. Appl. WO 2000036092 A2 20000622, 45 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US29873 19991216. PRIORITY: US 1998-PV112752 19981217.

AB Methods for high level expression of active lymphotoxin-.beta. receptor Ig chimeric proteins (LT.beta.R-Ig) and their purifn. are provided. The chimeric protein LT.beta.R-Ig contg. the **ligand** binding domain of lymphotoxin-.beta. receptor and Ig Fc domain linked by a spacer peptide are expressed in CHO cells and other protein expression systems. To increase the percentage of properly folded protein (live form), low temp. fermn. conditions are used. Hinge modification by site-specific mutagenesis to replace Cys101 and Cys108 to Ala in Ig Fc domain is also used to correct the folding problems of the fusion protein. Conventional hydrophobic interaction chromatog. can be used to sep. and quantitate the live proteins and dead proteins (protein mols. with **ligand** binding affinity substantially (10-1000 fold) lower than the natural or active form). The live protein can also be purified by monoclonal antibody affinity column. The analyses of purified secreted LT.beta.R-Ig or **HVEM**(**Herpesvirus entry mediator**)-Ig and their **ligand** binding activities are presented.

L6 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2002 ACS
2000:175929 Document No. 132:218642 Novel molecules of the herpes virus-entry-mediator-related protein family and their diagnostic and therapeutic uses. Busfield, Samantha J. (Millennium Biotherapeutics,

Inc., USA). PCT Int. Appl. WO 2000014230 A1 20000316, 151 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US20180 19990903. PRIORITY: US 1998-146950 19980903; US 1999-342767 19990629.

AB The present invention is based on the discovery of 3 cDNA mols. which encode sol. forms (sHVEM), and one cDNA mol. that encodes a second membrane-bound form, of the membrane-bound herpes virus entry mediator (mHVEM), a member of the tumor necrosis factor receptor superfamily. The 3 sHVEM sequences differ from mHVEM in 2 important ways: first they lac the C-terminal end of mHVEM which contains the transmembrane domain of mHVEM; and secondly, they have addnl. amino acids at their C-terminal ends that are not found at the C-terminal end of mHVEM. The **HVEM** mols. bind to LIGHT (also called TANGO-69) and lymphotoxin a, such that the mols. are also known as TANGO-69 receptors. Northern blot anal. revealed that an .apprx.2 kb sHVEM1 mRNA transcript is present at similar levels in stimulated and unstimulated mast cells, as well as in stimulated human umbilical vein endothelial cells (HUVECs), but not in unstimulated HUVECs. Tissue localization suggests that sHVEM1 can play a role in allergic reactions and can play an anti-inflammatory role in the endothelium. Mapping data places TANGO-69 receptor gene at human chromosome 1 region p36.2-p36.3, an area putatively syntenic to a region of mouse chromosome 4 near the IgE defective response locus. In addn. to isolated, full-length TANGO-69-receptor proteins, the invention further provides isolated TANGO-69-receptor fusion proteins, antigenic peptides and anti-TANGO-69-receptor antibodies. The invention also provides TANGO-69-receptor nucleic acid mols., recombinant expression vectors contg. a nucleic acid mol. of the invention, host cells into which the expression vectors have been introduced and non-human transgenic animals in which a TANGO-69-receptor gene has been introduced or disrupted. Diagnostic, screening and therapeutic methods utilizing compns. of the invention are also provided.

L6 ANSWER 9 OF 22 SCISEARCH COPYRIGHT 2002 ISI (R)

2000:943983 The Genuine Article (R) Number: 381AH. Overexpression of Bcl-2 enhances LIGHT- and interferon-gamma-mediated apoptosis in Hep3BT2 cells. Chen M C; Hsu T L; Luh T Y; Hsieh S L (Reprint). NATL YANG MING UNIV, INST MICROBIOL & IMMUNOL, TAIPEI 11221, TAIWAN (Reprint); NATL YANG MING UNIV, INST MICROBIOL & IMMUNOL, TAIPEI 11221, TAIWAN; NATL YANG MING UNIV, DEPT IMMUNOL & MICROBIOL, TAIPEI 11221, TAIWAN; NATL TAIWAN UNIV, DEPT CHEM, TAIPEI 11221, TAIWAN; NATL YANG MING UNIV, IMMUNOL RES CTR, TAIPEI 11221, TAIWAN. JOURNAL OF BIOLOGICAL CHEMISTRY (8 DEC 2000) Vol. 275, No. 49, pp. 38794-38801. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. ISSN: 0021-9258. Pub. country: TAIWAN. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB LIGHT is a member of the tumor necrosis factor superfamily and is the **Ligand** for LT-betaR, **HVEM**, and decoy receptor 3. LIGHT has a cytotoxic effect, which is further enhanced by the presence of interferon-gamma (IFN-gamma). Although LIGHT/IFN-gamma can activate caspase activity, neither benzyloxycarbonyl-Asp-Glu-Val-Asp-fluoromethylketone nor benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone can completely inhibit LIGHT/IFN-gamma -mediated apoptosis. Moreover, overexpression of Bcl-2 further enhances LIGHT/IFN-gamma -mediated apoptosis. It appears that LIGHT and IFN-gamma act synergistically to activate caspase-3, with the resultant cleavage of Bcl-2, removal of the BH4 domain, leading to conversion of Bcl-2 from an antiapoptotic to a proapoptotic form in p53-deficient hepatocellular carcinoma Hep3BT2 cells. Thus, LIGHT seems to be able to override the protective effect of Bcl-2 and induce cell death. Although benzyloxycarbonyl-Asp-Glu-Val-Asp-

fluoromethylketone and benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone can prevent the cleavage of Bcl-2 by LIGHT/IFN-gamma they only partially inhibit apoptosis in Hep3BT2 cells that are overexpressing Bcl-2. In contrast, both LIGHT/IFN-gamma -mediated apoptosis and Bcl-2 cleavage are inhibited by free radical scavengers, indicating that free radicals may play an essential role in LIGHT/IFN-gamma -mediated apoptosis at a step upstream of caspase-3 activation. These results suggest that LIGHT signaling may diverge into multiple, separate processes.

L6 ANSWER 10 OF 22 MEDLINE
2000487952 Document Number: 20491929. PubMed ID: 11035077. Reciprocal expression of the TNF family receptor herpes virus entry mediator and its **ligand** LIGHT on activated T cells: LIGHT down-regulates its own receptor. Morel Y; Schiano de Colella J M; Harrop J; Deen K C; Holmes S D; Wattam T A; Khandekar S S; Truneh A; Sweet R W; Gastaut J A; Olive D; Costello R T. (Laboratoire d'Immunologie des Tumeurs, Departement d'Hematologie, Institut Paoli Calmettes, Universite de la Mediterranee, Marseille, France.) JOURNAL OF IMMUNOLOGY, (2000 Oct 15) 165 (8) 4397-404. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB The TNF receptor (TNFR) family plays a central role in the development of the immune response. Here we describe the reciprocal regulation of the recently identified TNFR superfamily member herpes virus entry mediator (**HVEM**) (TR2) and its **ligand** LIGHT (TL4) on T cells following activation and the mechanism of this process. T cell activation resulted in down-regulation of **HVEM** and up-regulation of LIGHT, which were both more pronounced in CD8(+) than CD4(+) T lymphocytes. The analysis of **HVEM** and LIGHT mRNA showed an increase in the steady state level of both mRNAs following stimulation. LIGHT, which was present in cytoplasm of resting T cells, was induced both in cytoplasm and at the cell surface. For **HVEM**, activation resulted in cellular redistribution, with its disappearance from cell surface. **HVEM** down-regulation did not rely on de novo protein synthesis, in contrast to the partial dependence of LIGHT induction. Matrix metalloproteinase inhibitors did not modify **HVEM** expression, but did enhance LIGHT accumulation at the cell surface. However, **HVEM** down-regulation was partially blocked by a neutralizing mAb to LIGHT or an **HVEM** -Fc fusion protein during activation. As a model, we propose that following stimulation, membrane or secreted LIGHT binds to **HVEM** and induces receptor down-regulation. Degradation or release of LIGHT by matrix metalloproteinases then contributes to the return to baseline levels for both LIGHT and **HVEM**. These results reveal a self-regulating **ligand**/receptor system that contributes to T cell activation through the interaction of T cells with each other and probably with other cells of the immune system.

L6 ANSWER 11 OF 22 SCISEARCH COPYRIGHT 2002 ISI (R)
2000:298162 The Genuine Article (R) Number: 303GZ. LIGHT, a TNF-like molecule, costimulates T cell proliferation and is required for dendritic cell-mediated allogeneic T cell response. Tamada K; Shimozaki K; Chapoval A I; Zhai Y F; Su J; Chen S F; Hsieh S L; Nagata S; Ni J; Chen L P (Reprint). MAYO CLIN & MAYO FDN, DEPT IMMUNOL, 200 1ST ST SW, ROCHESTER, MN 55905 (Reprint); MAYO CLIN & MAYO GRAD SCH MED, DEPT IMMUNOL, ROCHESTER, MN 55905; MAYO CLIN & MAYO GRAD SCH MED, DEPT IMMUNOL, ROCHESTER, MN 55905; OSAKA UNIV, SCH MED, DEPT GENET, OSAKA, JAPAN; HUMAN GENOME SCI INC, ROCKVILLE, MD 20850; NATL YANG MING UNIV, SCH MED, DEPT MICROBIOL & IMMUNOL, TAIPEI 112, TAIWAN. JOURNAL OF IMMUNOLOGY (15 APR 2000) Vol. 164, No. 8, pp. 4105-4110. Publisher: AMER ASSOC IMMUNOLOGISTS. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. ISSN: 0022-1767. Pub. country: USA; JAPAN; TAIWAN. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB LIGHT is a recently identified member of the TNF superfamily and its receptors, **herpesvirus entry mediator** and lymphotoxin beta receptor, are found in T cells and stromal cells. In this study, me demonstrate that LIGHT is selectively expressed on immature

dendritic cells (DCs) generated from human PBMCs, In contrast, LIGHT is not detectable in DCs either freshly isolated from PBMCs or rendered mature in vitro by LPS treatment. Blockade of LIGHT by its soluble receptors, lymphotoxin beta receptor-Ig or **HVEM**-Ig, inhibits the induction of DC-mediated primary allogeneic T cell response. Furthermore, engagement of LIGHT costimulates human T cell proliferation, amplifies the NF-kappa B signaling pathway, and preferentially induces the production of IFN-gamma, but not IL-4, in the presence of an antigenic signal, Our results suggest that LIGHT is a costimulatory molecule involved in DC-mediated cellular immune responses.

L6 ANSWER 12 OF 22 MEDLINE DUPLICATE 5
1999253915 Document Number: 99253915. PubMed ID: 10318773. A newly identified member of tumor necrosis factor receptor superfamily (TR6) suppresses LIGHT-mediated apoptosis. Yu K Y; Kwon B; Ni J; Zhai Y; Ebner R; Kwon B S. (Department of Microbiology and Immunology and Walther Oncology Center, Indiana University School of Medicine and the Walther Cancer Institute, Indianapolis, Indiana 46202, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 May 14) 274 (20) 13733-6. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB TR6 (decoy receptor 3 (DcR3)) is a new member of the tumor necrosis factor receptor (TNFR) family. TR6 mRNA is expressed in lung tissues and colon adenocarcinoma, SW480. In addition, the expression of TR6 mRNA was shown in the endothelial cell line and induced by phorbol 12-myristate 13-acetate/ionomycin in Jurkat T leukemia cells. The open reading frame of TR6 encodes 300 amino acids with a 29-residue signal sequence but no transmembrane region. Using histidine-tagged recombinant TR6, we screened soluble forms of TNF-**ligand** proteins with immunoprecipitation. Here, we demonstrate that TR6 specifically binds two cellular **ligands**, LIGHT (herpes virus entry mediator (**HVEM**)-L) and Fas **ligand** (FasL/CD95L). These bindings were confirmed with HEK 293 EBNA cells transfected with LIGHT cDNA by flow cytometry. TR6 inhibited LIGHT-induced cytotoxicity in HT29 cells. It has been shown that LIGHT triggers apoptosis of various tumor cells including HT29 cells that express both lymphotoxin beta receptor (LTbetaR) and **HVEM**/TR2 receptors. Our data suggest that TR6 inhibits the interactions of LIGHT with **HVEM**/TR2 and LTbetaR, thereby suppressing LIGHT- mediated HT29 cell death. Thus, TR6 may play a regulatory role for suppressing in FasL- and LIGHT-mediated cell death.

L6 ANSWER 13 OF 22 SCISEARCH COPYRIGHT 2002 ISI (R)
1999:410801 The Genuine Article (R) Number: 198QZ. Tumor necrosis factor receptor and Fas signaling mechanisms. Wallach D (Reprint); Varfolomeev E E; Malinin N L; Goltsev Y V; Kovalenko A V; Boldin M P. WEIZMANN INST SCI, DEPT BIOL CHEM, IL-76100 REHOVOT, ISRAEL (Reprint). ANNUAL REVIEW OF IMMUNOLOGY (4 JUN 1999) Vol. 17, pp. 331-367. Publisher: ANNUAL REVIEWS INC. 4139 EL CAMINO WAY, PO BOX 10139, PALO ALTO, CA 94303-0139. ISSN: 0732-0582. Pub. country: ISRAEL. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Four members of the tumor necrosis factor (TNF) **ligand** family, TNF-alpha, LT-alpha, LT-beta, and LIGHT, interact with four receptors of the TNF/nerve growth factor family, the p55 TNF receptor (CD120a), the p75 TNF receptor (CD120b), the lymphotoxin beta receptor (LT beta R), and herpes virus entry mediator (**HVEM**) to control a wide range of innate and adaptive immune response functions. Of these, the most thoroughly studied are cell death induction and regulation of the inflammatory process. Fas/Apo1 (CD95), a receptor of the TNF receptor family activated by a distinct **ligand**, induces death in cells through mechanisms shared with CD120a. The last four years have seen a proliferation in knowledge of the proteins participating in the signaling by the TNF system and CD95. The downstream signaling molecules identified so far-caspases, phospholipases, the three known mitogen activated protein (MAP) kinase pathways, and the NF-kappa B activation cascade-mediate the effects of other inducers as well. However, the molecules that initiate these signaling events, including the death domain- and TNF receptor

associated factor (TRAF) domain-containing adapter proteins and the signaling enzymes associated with them, are largely unique to the TNF/nerve growth factor receptor family.

L6 ANSWER 14 OF 22 SCISEARCH COPYRIGHT 2002 ISI (R)

1999:680584 The Genuine Article (R) Number: 231EN. A homogenous 384-well high throughput screen for novel tumor necrosis factor receptor: **Ligand** interactions using time resolved energy transfer. Moore K J; Turconi S; MilesWilliams A; Djaballah H; Hurskainen P; Harrop J; Murray K J; Pope A J (Reprint). SMITHKLINE BEECHAM PHARMACEUT, DEPT MOL SCREENING TECHNOL, NEW FRONTIER SCI PK N, 3RD AVE, HARLOW CM19 5AW, ESSEX, ENGLAND (Reprint); SMITHKLINE BEECHAM PHARMACEUT, DEPT MOL SCREENING TECHNOL, HARLOW CM19 5AW, ESSEX, ENGLAND; SMITHKLINE BEECHAM PHARMACEUT, DEPT IMMUNOL, HARLOW CM19 5AW, ESSEX, ENGLAND; WALLAC OY, TURKU, FINLAND. JOURNAL OF BIOMOLECULAR SCREENING (AUG 1999) Vol. 4, No. 4, pp. 205-214. Publisher: MARY ANN LIEBERT INC PUBL. 2 MADISON AVENUE, LARCHMONT, NY 10538. ISSN: 1087-0571. Pub. country: ENGLAND; FINLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The herpes virus entry mediator (**HVEM**) receptor and its **ligand**, **HVEM**-L, are involved in both herpes simplex virus type-1 (HSV-1) herpes simplex virus type-2 (HSV-2) infection, and in T-cell activation such that antagonists of this interaction are expected to have utility in viral and inflammatory diseases, In this report we describe the configuration of a homogeneous 384-well assay based on time-resolved energy transfer from a europium chelate on the **HVEM** receptor to an allophycocyanin (APC) acceptor on the **ligand**, Specific time resolved emission from the acceptor is observed on receptor: **ligand** complex formation, The results of various direct and indirect labeling strategies are described. Several assay optimization experiments were necessary to obtain an assay that was robust to automation and file compound interference while sensitive to the effect of potential inhibitors. The signal was stable for more than 24 h at room temperature using the Eu3+ chelates, suggesting no dissociation of the lanthanide ion. The 384-well assay was readily automated and was able to identify more than 99.5% of known positive controls in the validation studies successfully. Screening identified both a series of known potent inhibitors and several structural classes of hits that readily deconvoluted to yield single compound inhibitors with the desired functional activity in secondary biological assays. The equivalence of the data in 384- and 1536-well formats indicates that routine implementation of 1536-well chelate-based energy transfer screening appears to be primarily limited by liquid handling rather than detection issues.

L6 ANSWER 15 OF 22 MEDLINE DUPLICATE 6

1998438532 Document Number: 98438532. PubMed ID: 9765287.

Herpesvirus entry mediator ligand (**HVEM**-L), a novel **ligand** for **HVEM**/TR2, stimulates proliferation of T cells and inhibits HT29 cell growth. Harrop J A; McDonnell P C; Brigham-Burke M; Lyn S D; Minton J; Tan K B; Dede K; Spampanato J; Silverman C; Hensley P; DiPrinzio R; Emery J G; Deen K; Eichman C; Chabot-Fletcher M; Truneh A; Young P R. (Department of Molecular and Cellular Immunology, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania 19406, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Oct 16) 273 (42) 27548-56. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB **Herpesvirus entry mediator** (**HVEM**), a member of the tumor necrosis factor (TNF) receptor family, mediates herpesvirus entry into cells during infection. Upon overexpression, **HVEM** activates NF-kappaB and AP-1 through a TNF receptor-associated factor (TRAF)-mediated mechanism. Using an **HVEM**-Fc fusion protein, we screened soluble forms of novel TNF-related proteins derived from an expressed sequence tag data base. One of these, which we designated **HVEM**-L, specifically bound to **HVEM**-Fc with an affinity of 44 nM. This association was confirmed with soluble and membrane forms of both receptor and **ligand**.

HVEM-L mRNA is expressed in spleen, lymph nodes, macrophages, and T cells and encodes a 240-amino acid protein. A soluble, secreted form of the protein stimulates proliferation of T lymphocytes during allogeneic responses, inhibits HT-29 cell growth, and weakly stimulates NF-kappaB-dependent transcription.

L6 ANSWER 16 OF 22 SCISEARCH COPYRIGHT 2002 ISI (R)
1998:762711 The Genuine Article (R) Number: 121HC. LIGHT, a new pro-apoptotic cytokine member of the TNF superfamily, and lymphotoxin-alpha are **ligands** for the **herpesvirus entry mediator** (**HVEM**).. Mauri D (Reprint); Ebner R; Montgomery R; Kochel K; Cheung T C; Yu G L; Ruben S; Murphy M; Eisenberg R J; Cohen G H; Spear P G; Ware C F. LA JOLLA INST ALLERGY & IMMUNOL, SAN DIEGO, CA 92121; HUMAN GENOME SCI INC, ROCKVILLE, MD 20850; NORTHWESTERN UNIV, CHICAGO, IL 60611; UNIV PENN, PHILADELPHIA, PA 19104. FASEB JOURNAL (17 MAR 1998) Vol. 12, No. 4, Part 1, Supp. [S], pp. 1754-1754. Publisher: FEDERATION AMER SOC EXP BIOL. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 . ISSN: 0892-6638. Pub. country: USA. Language: English.

L6 ANSWER 17 OF 22 MEDLINE
1998411370 Document Number: 98411370. PubMed ID: 9739048. LIGHT, a novel **ligand** for lymphotoxin beta receptor and TR2/**HVEM** induces apoptosis and suppresses in vivo tumor formation via gene transfer. Zhai Y; Guo R; Hsu T L; Yu G L; Ni J; Kwon B S; Jiang G W; Lu J; Tan J; Ugustus M; Carter K; Rojas L; Zhu F; Lincoln C; Endress G; Xing L; Wang S; Oh K O; Gentz R; Ruben S; Lippman M E; Hsieh S L; Yang D. (Human Genome Sciences, Inc., Rockville, Maryland 20850, USA.) JOURNAL OF CLINICAL INVESTIGATION, (1998 Sep 15) 102 (6) 1142-51. Journal code: HS7; 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.
AB LIGHT is a new member of tumor necrosis factor (TNF) cytokine family derived from an activated T cell cDNA library. LIGHT mRNA is highly expressed in splenocytes, activated PBL, CD8(+) tumor infiltrating lymphocytes, granulocytes, and monocytes but not in the thymus and the tumor cells examined. Introduction of LIGHT cDNA into MDA-MB-231 human breast carcinoma caused complete tumor suppression in vivo. Histological examination showed marked neutrophil infiltration and necrosis in LIGHT expressing but not in the parental or the Neo-transfected MDA-MB-231 tumors. Interferon gamma (IFNgamma) dramatically enhances LIGHT-mediated apoptosis. LIGHT protein triggers apoptosis of various tumor cells expressing both lymphotoxin beta receptor (LTbetaR) and TR2/**HVEM** receptors, and its cytotoxicity can be blocked specifically by addition of a LTbetaR-Fc or a TR2/**HVEM**-Fc fusion protein. However, LIGHT was not cytolytic to the tumor cells that express only the LTbetaR or the TR2/**HVEM** or hematopoietic cells examined that express only the TR2/**HVEM**, such as PBL, Jurkat cells, or CD8(+) TIL cells. In contrast, treatment of the activated PBL with LIGHT resulted in release of IFNgamma. Our data suggest that LIGHT triggers distinct biological responses based on the expression patterns of its receptors on the target cells. Thus, LIGHT may play a role in the immune modulation and have a potential value in cancer therapy.

L6 ANSWER 18 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1998:200127 Document No.: PREV199800200127. Light, a new pro-apoptotic cytokine member of the TNF superfamily, and lymphotoxin-alpha are **ligands** for the **herpesvirus entry mediator** (**HVEM**. Mauri, D. (1); Ebner, R.; Montgomery, R.; Kochel, K. (1); Cheung, T. C. (1); Yu, G.-L.; Ruben, S.; Murphy, M.; Eisenberg, R. J.; Cohen, G. H.; Spear, P. G.; Ware, C. F. (1). (1) La Jolla Inst. Allergy and Immunol., San Diego, CA 92121 USA. FASEB Journal, (March 17, 1998) Vol. 12, No. 4, pp. A301. Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology 98, Part 1 San Francisco, California, USA April 18-22, 1998 Federation of American Societies for Experimental Biology. ISSN: 0892-6638. Language: English.

L6 ANSWER 19 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

1998:458023 Document No.: PREV199800458023. **HVEM**-L, a novel **ligand** for **HVEM**/TR2, stimulates NF-kappaB dependent transcription and T cell proliferation. Harrop, J.; McDonnell, P.; Brigham-Burke, M.; Lyn, S.; Minton, J.; Tan, K. B.; Dede, K.; Spampanato, J.; Silverman, C.; Hensley, P.; Diprinzio, R.; Emery, J.; Eichman, C.; Chabot-Fletcher, M.; Truneh, A.; Young, P.. SmithKline Beecham Pharmaceutical, King of Prussia, PA USA. Journal of Interferon and Cytokine Research, (May, 1998) Vol. 18, No. 5, pp. A39. Meeting Info.: 7th International Conference on Tumor Necrosis Factor and Related Molecules Scientific Advances and Medical Applications Hyannis, Massachusetts, USA May 17-21, 1998 ISSN: 1079-9907. Language: English.

L6 ANSWER 20 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

1998:458017 Document No.: PREV199800458017. Lymphotoxins meet herpesvirus: New light on the darkside of virus-host interactions. Ware, C. F. (1); Mauri, D. M. (1); Ebner, R.; Montgomery, R. I.; Kochel, K. D. (1); Cheung, T. C. (1); Yu, G.-L.; Ruben, S.; Murphy, M.; Eisenberg, R. J.; Cohen, G. H.; Spear, P. G.. (1) La Jolla Inst. Allergy Immunol., San Diego, CA 92121 USA. Journal of Interferon and Cytokine Research, (May, 1998) Vol. 18, No. 5, pp. A36. Meeting Info.: 7th International Conference on Tumor Necrosis Factor and Related Molecules Scientific Advances and Medical Applications Hyannis, Massachusetts, USA May 17-21, 1998 ISSN: 1079-9907. Language: English.

L6 ANSWER 21 OF 22 MEDLINE DUPLICATE 7

1998122340 Document Number: 98122340. PubMed ID: 9462508. LIGHT, a new member of the TNF superfamily, and lymphotoxin alpha are **ligands** for **herpesvirus entry mediator**. Mauri D N; Ebner R; Montgomery R I; Kochel K D; Cheung T C; Yu G L; Ruben S; Murphy M; Eisenberg R J; Cohen G H; Spear P G; Ware C F. (Division of Molecular Immunology, La Jolla Institute for Allergy and Immunology, San Diego, California 92121, USA.) IMMUNITY, (1998 Jan) 8 (1) 21-30. Journal code: CCF; 9432918. ISSN: 1074-7613. Pub. country: United States. Language: English.

AB Herpes simplex virus (HSV) 1 and 2 infect activated T lymphocytes by attachment of the HSV envelope glycoprotein D (gD) to the cellular **herpesvirus entry mediator** (**HVEM**), an orphan member of the tumor necrosis factor receptor superfamily. Here, we demonstrate that **HVEM** binds two cellular **ligands**, secreted lymphotoxin alpha (LTalpha) and LIGHT, a new member of the TNF superfamily. LIGHT is a 29 kDa type II transmembrane protein produced by activated T cells that also engages the receptor for the LTalphabeta heterotrimer but does not form complexes with either LTalpha or LTbeta. HSV1 gD inhibits the interaction of **HVEM** with LIGHT, and LIGHT and gD interfere with **HVEM**-dependent cell entry by HSV1. This characterizes herpesvirus gD as a membrane-bound viokine and establishes LIGHT-**HVEM** as integral components of the lymphotoxin cytokine-receptor system.

L6 ANSWER 22 OF 22 CAPLUS COPYRIGHT 2002 ACS

1998:29120 Document No. 128:165342 Characterization of a novel TNF-like **ligand** and recently described TNF **ligand** and TNF receptor superfamily genes and their constitutive and inducible expression in hematopoietic and non-hematopoietic cells. Tan, K. B.; Harrop, Jeremy; Reddy, Manjula; Young, Peter; Terrett, Jonathan; Emery, John; Moore, Gordon; Truneh, Alemseged (Department Molecular Immunology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406-0939, USA). Gene, 204(1/2), 35-46 (English) 1997. CODEN: GENED6. ISSN: 0378-1119. Publisher: Elsevier Science B.V..

AB A novel (TL1), a recently described (TL2) TNF-like, and three recently described TNF receptor-like (TR1, TR2, TR3) mols. were identified by searching a cDNA database. TL1 and TL2 are type-II membrane proteins. TR2 and TR3 and type-I membrane proteins whereas TR1 appears to be a secreted protein. TL1, TL2, TR2 and TR3 were expressed in hematopoietic cells, whereas TR1 was not. Northern blots hybridized with the cDNA

probes revealed multiple forms of RNA as well as inducible expression of TL1, TL2, TR2 and TR3. TL2 and TR3, in particular, were highly induced in activated CD4+ T cells. Radiation hybrid mapping localized TR1 and TL2 to 8q24 and 3q26, resp., which are not near any known superfamily members. TL1 was mapped to 9q32, near CD30L (9q33) and TR2 and TR3 mapped to the region of chromosome 1 that contains the TNFR-II, 4-1BB, OX40 and CD30 gene cluster at 1p36. Only TR3 in this cluster possesses a death domain. Southern blot anal. revealed the presence of TL and TR genes in different mammalian species. TL2, TR1, TR2 and TR3 were recently described by others as TRAIL/Apo-2L, OPG, **HVEM** and DR3/WSL-1/Apo-3/TRAMP/LARD, resp.

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=> s lymphotoxix alpha
L7            0 LYMPHOTOXIX ALPHA

=> s lymphotoxin alpha
L8         1344 LYMPHOTOXIN ALPHA

=> s l8 and proliferation
L9           99 L8 AND PROLIFERATION

=> s l9 and soluble
L10          29 L9 AND SOLUBLE

=> dup remove l10
PROCESSING COMPLETED FOR L10
L11           9 DUP REMOVE L10 (20 DUPLICATES REMOVED)

=> d l11 1-9 cbib abs
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L11 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2002 ACS
2001:367950 Document No. 135:151367 Recombinant, **soluble** LIGHT (HVEM ligand) induces increased IL-8 secretion and growth arrest in A375 melanoma cells. Hehlgans, Thomas; Mannel, Daniela N. (Institute of Pathology/Tumor Immunology, University of Regensburg, Germany). J. Interferon Cytokine Res., 21(5), 333-338 (English) 2001. CODEN: JICRFJ. ISSN: 1079-9907. Publisher: Mary Ann Liebert, Inc..

AB The heterotrimeric **lymphotoxin .alpha.**1.beta.2 (LT.alpha.1.beta.2) complex and LIGHT, a new member of the tumor necrosis factor (TNF) superfamily, have been identified as membrane-anchored ligands for the LT.beta. receptor (LT.beta.R), a member of the TNF receptor (TNFR) superfamily. Although some of the biol. activities of this receptor have been described using either **sol.** LT.alpha.1.beta.2 as a ligand or agonistic monoclonal antibodies (mAb), very little is known about the signaling of LIGHT via the LT.beta.R. To gain more insight into the biol. functions of LIGHT, the authors generated a recombinant **sol.** form of human LIGHT (rsHuLIGHT). The authors demonstrate here that this rsHuLIGHT is capable of binding to the LT.beta.R. Interestingly, receptor-mediated ligand pptn. anal. revealed that rsHuLIGHT bound only to human LT.beta.R but not to mouse LT.beta.R, indicating a species-specific receptor ligand interaction. Activation of A375 human melanoma cells by rsHuLIGHT induced an increased secretion of interleukin-8 (IL-8). Furthermore, rsHuLIGHT caused growth arrest of A375 cells even in the absence of interferon-.gamma. (IFN-.gamma.).

L11 ANSWER 2 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998362501 EMBASE Generation of splenic follicular structure and B cell movement in tumor necrosis factor-deficient mice. Cook M.C.; Korner H.; Riminton D.S.; Lemckert F.A.; Hasbold J.; Amesbury M.; Hodgkin P.D.; Cyster J.G.; Sedgwick J.D.; Basten A.. A. Basten, Can. Med./Cell Biol. Centenary Inst., Bldg. 93, Royal Prince Alfred Hospital, Missenden Rd., Camperdown, NSW 2050, Australia. a.basten@centenary.usyd.edu.au. Journal of Experimental Medicine 188/8 (1503-1510) 19 Oct 1998.
Refs: 34.

ISSN: 0022-1007. CODEN: JEMEAV. Pub. Country: United States. Language: English. Summary Language: English.

AB Secondary lymphoid tissue organogenesis requires tumor necrosis factor (TNF) and **lymphotoxin .alpha.** (LT.alpha.). The role of TNF in B cell positioning and formation of follicular structure was studied by comparing the location of newly produced naive recirculating and antigen-stimulated B cells in TNF(-/-) and TNF/LT.alpha.(-/-) mice. By creating radiation bone marrow chimeras from wild-type and TNF(-/-) mice, formation of normal splenic B cell follicles was shown to depend on TNF production by radiation-sensitive cells of hemopoietic origin. Reciprocal adoptive transfers of mature B cells between wild-type and knockout mice indicated that normal follicular tropism of recirculating naive B cells occurs independently of TNF derived from the recipient spleen. Moreover, **soluble** TNF receptor-IgG fusion protein administered in vivo failed to prevent B cell localization to the follicle or the germinal center reaction. Normal T zone tropism was observed when antigen-stimulated B cells were transferred into TNF(-/-) recipients, but not into TNF/LT.alpha.(-/-) recipients. This result appeared to account for the defect in isotype switching observed in intact TNF/LT.alpha.(-/-) mice because TNF/LT.alpha.(-/-) B cells, when stimulated in vitro, switched isotypes normally. Thus, TNF is necessary for creating the permissive environment for B cell movement and function, but is not itself responsible for these processes.

L11 ANSWER 3 OF 9 MEDLINE DUPLICATE 1

1998444390 Document Number: 98444390. PubMed ID: 9767423. **Lymphotoxin-alpha** is an important autocrine factor for CD40 + interleukin-4-mediated B-cell activation in normal and atopic donors. Worm M; Ebermayer K; Henz B. (Department of Dermatology, Charite-Virchow Klinikum, Humboldt Universitat, Berlin, Germany.) IMMUNOLOGY, (1998 Jul) 94 (3) 395-402. Journal code: GH7; 0374672. ISSN: 0019-2805. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Stimulation of human B cells with anti-CD40 + interleukin-4 (IL-4) results not only in **proliferation** and immunoglobulin E (IgE)-production, but also increased production of the cytokine **lymphotoxin-alpha** (LT-alpha) (formerly also known as tumour necrosis factor-beta (TNF-beta)). Here, we studied the role of LT-alpha (TNF-beta) in B cells following stimulation with anti-CD40 + IL-4 from normal versus atopic donors. Anti-CD40 + IL-4 stimulation of peripheral blood mononuclear cells (PBMC) from atopic donors resulted in enhanced production of **soluble** LT-alpha (TNF-beta) and increased membrane LT-alpha (TNF-beta) expression on the B cells compared with normal donors. Functional evaluation of LT-alpha (TNF-beta) in CD40 + IL-4-stimulated B cells shows that recombinant LT-alpha (TNF-beta) induces **proliferation** of B cells and enhances CD40 + IL-4-mediated B-cell **proliferation** and IgE synthesis in both normal and atopic donors in a dose-dependent manner. These findings were supported by semiquantitative analysis of epsilon-germline transcripts using reverse transcription-polymerase chain reaction (RT-PCR) showing increased epsilon-germline transcription in the presence of LT-alpha. Furthermore, addition of anti-LT-alpha (anti-TNF-beta) to CD40 + IL-4-stimulated B cells partially inhibited **proliferation** and IgE synthesis in a dose-dependent manner indicating a role of endogenous LT-alpha (TNF-beta) production by B cells during continued CD40 + IL-4 stimulation. These data suggest that LT-alpha (TNF-beta) plays a potentially significant role during B-cell **proliferation** and IgE synthesis. Moreover, LT-alpha (TNF-beta) production seems to be differentially regulated in B cells from normal and atopic donors.

L11 ANSWER 4 OF 9 MEDLINE DUPLICATE 2

97272117 Document Number: 97272117. PubMed ID: 9126962. Involvement of IL-10 in the autonomous growth of EBV-transformed B cell lines. Beatty P R; Krams S M; Martinez O M. (Department of Surgery, Stanford University Medical Center, CA 94305, USA.) JOURNAL OF IMMUNOLOGY, (1997 May 1) 158 (9) 4045-51. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country:

United States. Language: English.

AB Immunocompromised individuals have an increased incidence of EBV-associated B cell lymphomas. The growth factors responsible for the unrestrained **proliferation** of these lymphomas have not yet been determined. In this study, spontaneous lymphoblastoid cell lines (SLCL) were derived without the addition of growth factors or virus from four patients with EBV-associated lymphoproliferative disorder. These cell lines were EBV transformed in vivo, and infection was verified through amplification of the viral gp220 gene. SLCL have an activated B cell phenotype (CD19+, CD21+, CD23+, CD38+, and CD40+) and produce IL-6, IL-10, TNF-alpha, and **lymphotoxin-alpha**. To determine whether these cytokines contribute to autonomous growth, neutralizing Abs for IL-10, IL-6, and TNF-alpha, a **soluble** TNFR:Fc fusion protein, and **soluble** IL-10R were used. These experiments established that, of the cytokines produced by SLCL, only IL-10 is an autocrine factor. IL-10 was produced by the majority of cells within each SLCL, and IL-10 secretion was concomitant with SLCL growth. Our findings demonstrate that IL-10 is utilized in the autonomous growth of EBV-related lymphomas and may be crucial in the development of lymphoproliferative disorder.

L11 ANSWER 5 OF 9 MEDLINE DUPLICATE 3

96394666 Document Number: 96394666. PubMed ID: 8798772. Lymphotoxin beta receptor triggering induces activation of the nuclear factor kappaB transcription factor in some cell types. Mackay F; Majeau G R; Hochman P S; Browning J L. (Department of Cell Biology, Biogen Inc., Cambridge, Massachusetts 02142, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Oct 4) 271 (40) 24934-8. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB NFkappaB is a pleiotropic transcription factor capable of activating the expression of a great variety of genes critical for the immunoinflammatory response. Tumor necrosis factor alpha (TNFalpha) and **lymphotoxin alpha** (LTalpha, originally TNFbeta) are potent nuclear factor kappaB (NFkappaB) activators in various cell types. The LTalpha molecule, in addition to being secreted as a **soluble** trimer, can also form membrane-anchored heterotrimers with the LTbeta chain, another member of the TNF family. The LTalpha1beta2 heterotrimer binds a specific receptor, called the LTbeta receptor (LTbeta-R), which is also a member of the TNF receptor family. Here, we show that engagement of LTbeta-R with a **soluble** form of LTalpha1beta2 or with a specific anti-LTbeta-R agonistic monoclonal antibody CBE11 quickly induces activation of NFkappaB in HT-29 and WiDr human adenocarcinomas. LTbeta-R triggering activates NFkappaB and induces **proliferation** in WI-38 human lung fibroblasts. No NFkappaB activation is observed in human umbilical vein endothelial cells, correlating with the inability of LTbeta-R activation to induce expression of NFkappaB-dependent cell surface adhesion molecules. Thus, like several other members of the TNF receptor family, the LTbeta-R can activate NFkappaB following receptor ligation in some but not all LTbeta-R-positive cells.

L11 ANSWER 6 OF 9 MEDLINE DUPLICATE 4

97163923 Document Number: 97163923. PubMed ID: 9010678. Production of prostaglandin E2 and collagenase is inhibited by the recombinant **soluble** tumour necrosis factor receptor p55-human gamma 3 fusion protein at concentrations a hundred-fold lower than those decreasing T cell activation. Nicod L P; Isler P; Chicheportiche R; Songeon F; Dayer J M. (Respiratory Division, University Hospital, Geneva, Switzerland.) EUROPEAN CYTOKINE NETWORK, (1996 Dec) 7 (4) 757-63. Journal code: A56; 9100879. ISSN: 1148-5493. Pub. country: France. Language: English.

AB TNF-alpha and **lymphotoxin alpha** (TNF-beta) are pleiotropic cytokines with regulatory functions in inflammatory reactions and T cell activation. Natural TNF inhibitors such as **soluble** TNF-binding proteins, i.e. TNFsR55 and TNFsR75, are shed from white blood cells and probably other cells. These naturally occurring inhibitors of TNF are shown to be 10 times less effective than the bivalent antagonist of TNF, recombinant **soluble** TNF receptor p55-human gamma 3

fusion protein (rsTNFR-p55h gamma 3), in controlling the release of prostaglandin E2 (PGE2) and collagenase by fibroblasts, as well as in controlling T cell **proliferation**. In order to block the action of rhTNF-alpha added to fibroblasts, a fivefold excess of rsTNFR-p55h gamma 3 was sufficient, but concentrations of a hundred to a thousand times higher were required to obtain a significant inhibition of T cell activation. This concentration appears to be required to block membrane-bound TNF-alpha on peripheral blood mononuclear cells as shown by Scatchard analysis. We additionally show that rsTNFR-p55h gamma 3 at high concentrations also blocks T cell activation by dendritic cells. In conclusion rsTNFR-p55h gamma 3 has a much higher anti-inflammatory effect than immunosuppressive effect.

L11 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2002 ACS
1997:133820 Document No. 126:224097 Production of prostaglandin E2 and collagenase is inhibited by the recombinant **soluble** tumor necrosis factor receptor p55-human .gamma.3 fusion protein at concentrations a hundred-fold lower than those decreasing T cell activation. Nicod, L. P.; Isler, P.; Chicheportiche, R.; Songeon, F.; Dayer, J.-M. (Rekspiratory Div., Univ. Hospital, Geneva, Switz.). Eur. Cytokine Network, 7(4), 755-763 (English) 1996. CODEN: ECYNEJ. ISSN: 1148-5493. Publisher: Libbey Eurotext.
AB TNF-.alpha. and **lymphotoxin .alpha.** (TNF-.beta.) are pleiotropic cytokines with regulatory functions in inflammatory reactions and T cell activation. Natural TNF inhibitors such as **sol**. TNF-binding proteins, i.e. TNFsR55 and TNFsR75, are shed from white blood cells and probably other cells. These naturally occurring inhibitors of TNF are shown to be 10 times less effective than the bivalent antagonist of TNF, recombinant **sol**. TNF receptors p55-human .gamma.3 fusion protein (rsTNFR-p55h.gamma.3), in controlling the release of prostaglandin E2 (PGE2) and collagenase by fibroblasts, as well controlling T cell **proliferation**. To block the action of rhTNF-.alpha. added to fibroblasts, a fivefold excess of rsTNFR-p55h.gamma.3 was sufficient, but concns. of a hundred to a thousand times higher were required to obtain a significant inhibition of T cell activation. This concn. appears to be required to block membrane-bound TNF-.alpha. on peripheral blood mononuclear cells as shown by Scatchard anal. We addnl. show rsTNFR-p55.gamma.3 at high concns. also blocks T cell activation by dendritic cells. In conclusions rsTNFR-p55h.gamma.3 has a much higher anti-inflammatory effect than immunosuppressive effect.

L11 ANSWER 8 OF 9 MEDLINE DUPLICATE 5
96131874 Document Number: 96131874. PubMed ID: 8589998. 2 A crystal structure of an extracellular fragment of human CD40 ligand. Karpusas M; Hsu Y M; Wang J H; Thompson J; Lederman S; Chess L; Thomas D. (Biogen, Inc., Cambridge, MA 02142, USA.) STRUCTURE, (1995 Oct 15) 3 (10) 1031-9. Journal code: B31; 9418985. ISSN: 0969-2126. Pub. country: ENGLAND: United Kingdom. Language: English.
AB BACKGROUND: The CD40 ligand (CD40L) is a member of the tumor necrosis factor (TNF) family of proteins and is transiently expressed on the surface of activated T cells. The binding of CD40L to CD40, which is expressed on the surface of B cells, provides a critical and unique pathway of cellular activation resulting in antibody isotype switching, regulation of apoptosis, and B cell **proliferation** and differentiation. Naturally occurring mutations of CD40L result in the clinical hyper-IgM syndrome, characterized by an inability to produce immunoglobulins of the IgG, IgA and IgE isotypes. RESULTS: We have determined the crystal structure of a **soluble** extracellular fragment of human CD40L to 2 A resolution and with an R factor of 21.8%. Although the molecule forms a trimer similar to that found for other members of the TNF family, such as TNF alpha and **lymphotoxin-alpha**, and exhibits a similar overall fold, there are considerable differences in several loops including those predicted to be involved in CD40 binding. CONCLUSIONS: The structure suggests that most of the hyper-IgM syndrome mutations affect the folding and stability of the

molecule rather than the CD40-binding site directly. Despite the fact that the hyper-IgM syndrome mutations are dispersed in the primary sequence, a large fraction of them are clustered in space in the vicinity of a surface loop, close to the predicted CD40-binding site.

L11 ANSWER 9 OF 9 MEDLINE DUPLICATE 6
95210205 Document Number: 95210205. PubMed ID: 7535097. CD40 ligation induces **lymphotoxin alpha** gene expression in human B cells. Worm M; Geha R S. (Division of Immunology, Children's Hospital, Harvard Medical School, Boston, MA 02115.) INTERNATIONAL IMMUNOLOGY, (1994 Dec) 6 (12) 1883-90. Journal code: AY5; 8916182. ISSN: 0953-8178. Pub. country: ENGLAND: United Kingdom. Language: English.
AB CD40 plays an important role in T cell mediated B cell **proliferation** and isotype switching. The cytokines tumor necrosis factor (TNF)-alpha and lymphotoxin (LT)-alpha are expressed by B cells, and are known to play a role in B cell activation. We have studied TNF-alpha and LT-alpha expression in human tonsillar B cells following stimulation with anti-CD40 mAb. Anti-CD40 induced weak TNF-alpha mRNA expression but strong LT-alpha mRNA expression and had little effect on the constitutive expression of LT-beta mRNA in B cells. Induction of TNF-alpha mRNA was inhibited by actinomycin D suggesting that CD40 ligation results in transcriptional activation of the TNF-alpha and LT-alpha genes. Anti-CD40 caused minimal increase in the expression of TNF-alpha on the B cell membrane and no detectable secretion of TNF-alpha. Anti-CD40 as well as **soluble** CD40 ligand caused sustained induction of LT-alpha on the membrane of the B cells lasting up to 120 h but induced no detectable secretion of LT-alpha. IL-4, a cytokine known to synergize with anti-CD40 in inducing B cell **proliferation** and isotype switching, augmented the induction of LT-alpha mRNA and of mLT-alpha expression by anti-CD40. These results indicate that CD40 ligation vigorously induces expression of membrane LT-alpha in B cells and that membrane LT-alpha may play a role in CD40 mediated B cell activation.

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=> s lymphotoxin beta receptor
L12         516 LYMPHOTOXIN BETA RECEPTOR

=> s l12 and soluble
L13          71 L12 AND SOLUBLE

=> s l71 and proliferation
L71 NOT FOUND
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of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s l13 and proliferation
L14          15 L13 AND PROLIFERATION

=> dup remove l14
PROCESSING COMPLETED FOR L14
L15            8 DUP REMOVE L14 (7 DUPLICATES REMOVED)

=> d l15 1-8 cbib abs

L15 ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2002 ACS
2001:781125  Document No. 135:343309  Ligand p30/LIGHT for HVEM (herpes virus
     entry mediator) and methods of therapeutic use.  Ware, Carl F. (La Jolla
     Institute for Allergy and Immunology, USA).  PCT Int. Appl. WO 2001079496
     A2 20011025, 104 pp.  DESIGNATED STATES: W:  AE, AG, AL, AM, AT, AU, AZ,
     BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES,
     FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,
     LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL,
     PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
     VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ,
     CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC,
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ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US11857 20010411. PRIORITY: US 2000-524325 20000313; US 2000-549096 20000412.

AB A novel polypeptide ligand, p30, for HVEM (herpes virus entry mediator) and functional variations and fragments thereof are provided. The HVEM ligand is isolated from II-23.D7 cell line, a human CD4+ T cell hybridoma. P30, which can be found as a membrane protein and can function as a cytokine, is also called LIGHT, because this polypeptide is homologous to Lymphotoxins, exhibits Inducible expression, and competes with HSV Glycoprotein D for HVEM, a receptor expressed by T lymphocytes. Because LIGHT can compete with HSV glycoprotein D for HVEM, homo-trimeric **sol**. forms of this polypeptide can be used to block the entry of herpesvirus into cells. P30 is useful for modulating immune responses and in inhibiting infection and/or subsequent **proliferation** by herpesvirus. LIGHT also bind to the **lymphotoxin-.beta** . **receptor** (LT.beta.R). The present invention is also based upon the discovery that HVEM polypeptides have an antagonistic effect on inflammation. In particular, HVEM fusion proteins are capable of inhibiting inflammation when administered to a subject. HVEM-Fc fusion proteins are also provided. Methods for treating subjects with lymphoid cell disorders, tumors, autoimmune diseases, inflammatory disorders of those having or suspected of having a herpes virus infection, utilizing p30 and the fusion proteins of the invention, are also provided.

L15 ANSWER 2 OF 8 SCISEARCH COPYRIGHT 2002 ISI (R)

2001:820221 The Genuine Article (R) Number: 479PC. Suppression by apoptotic cells defines tumor necrosis factor-mediated induction of glomerular mesangial cell apoptosis by activated macrophages. Duffield J S (Reprint); Ware C F; Ryffel B; Savill J. Univ Edinburgh, Sch Med, Ctr Inflammat Res, MRC, Teviot Pl, Edinburgh EH8 9AG, Midlothian, Scotland (Reprint); Univ Edinburgh, Sch Med, Ctr Inflammat Res, MRC, Edinburgh EH8 9AG, Midlothian, Scotland; Univ Calif San Diego, La Jolla Inst Allergy & Immunol, San Diego, CA 92103 USA; Univ Cape Town, Dept Med, ZA-7925 Cape Town, South Africa. AMERICAN JOURNAL OF PATHOLOGY (OCT 2001) Vol. 159, No. 4, pp. 1397-1404. Publisher: AMER SOC INVESTIGATIVE PATHOLOGY, INC. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3993 USA. ISSN: 0002-9440. Pub. country: Scotland; USA; South Africa. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Activated macrophages (M phi) isolated from inflamed glomeruli or generated by interferon-gamma and lipopolysaccharide treatment in vitro induce glomerular mesangial cell apoptosis by hitherto incompletely understood mechanisms. in this report we demonstrate that nitric oxide-independent killing of co-cultured mesangial cells by interferon-gamma /lipopolysaccharide-activated M phi is suppressed by binding/ingestion of apoptotic cells and is mediated by rumor necrosis factor (TNF). Thus, **soluble** TNF receptor-1 significantly inhibited induction of mesangial cell apoptosis by 1) rodent M phi in the presence of nitric oxide synthase inhibitors or 2) human M phi both situations in which nitric oxide release was minimal. Furthermore, murine TNF knockout M phi were completely unable to induce mesangial cell apoptosis in the presence of nitric oxide synthase inhibitors. We conclude that TNF-restricted M phi -directed apoptosis of glomerular mesangial cells can be down-regulated by M phi binding/ingestion of apoptotic cells, suggesting a new mechanism for negative feedback regulation of M phi controls on resident cell number at inflamed sites.

L15 ANSWER 3 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

2001:265922 Document No.: PREV200100265922. TNFRSF19L, a new member of tumor necrosis factor receptor superfamily, that is expressed in lymphoid organs and activates NF-kappaB. Sica, Gabriel (1); Zhu, Gefeng (1); Tamada, Koji (1); Liu, Ding; Ni, Jian; Chen, Lieping (1). (1) Mayo Clinic, 200 1st Street SW, Rochester, MN, 55905 USA. FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A700. print. Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001 ISSN:

0892-6638. Language: English. Summary Language: English.

AB We have cloned a new member of the TNFR superfamily, TNFRSF19L (Tumor Necrosis Factor Receptor Superfamily 19 Like). TNFRSF19L is a type I transmembrane glycoprotein with a cysteine rich extracellular domain that shares significant homology to TNFRSF19, decoy receptor 3, OX40, and **lymphotoxin beta receptor**. The mRNA of TNFRSF19L is especially abundant in lymphoid organs such as spleen, lymph node, and peripheral blood leukocytes as well as in leukemias and lymphomas. Overexpression of TNFRSF19L in 293 cells leads to the activation of the NF-kappaB pathway that is independent of TRAF 1, 2, 3, 5 and 6 binding. While the **soluble** form of TNFRSF19L fusion protein does not inhibit the one way mixed lymphocyte reaction, immobilized TNFRSF19L is capable of costimulating T cell **proliferation** in the presence of CD3 signaling. Our results define a new member of the TNFR superfamily that may be a potential regulator for immune responses.

L15 ANSWER 4 OF 8 MEDLINE DUPLICATE 1

2000219245 Document Number: 20219245. PubMed ID: 10754304. LIGHT, a TNF-like molecule, costimulates T cell **proliferation** and is required for dendritic cell-mediated allogeneic T cell response. Tamada K; Shimozaki K; Chapoval A I; Zhai Y; Su J; Chen S F; Hsieh S L; Nagata S; Ni J; Chen L. (Department of Immunology, Mayo Graduate and Medical Schools, Mayo Clinic, Rochester, MN 55905, USA.) JOURNAL OF IMMUNOLOGY, (2000 Apr 15) 164 (8) 4105-10. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB LIGHT is a recently identified member of the TNF superfamily and its receptors, herpesvirus entry mediator and **lymphotoxin beta receptor**, are found in T cells and stromal cells. In this study, we demonstrate that LIGHT is selectively expressed on immature dendritic cells (DCs) generated from human PBMCs. In contrast, LIGHT is not detectable in DCs either freshly isolated from PBMCs or rendered mature in vitro by LPS treatment. Blockade of LIGHT by its **soluble** receptors, **lymphotoxin beta receptor**-Ig or HVEM-Ig, inhibits the induction of DC-mediated primary allogeneic T cell response. Furthermore, engagement of LIGHT costimulates human T cell **proliferation**, amplifies the NF-kappaB signaling pathway, and preferentially induces the production of IFN-gamma, but not IL-4, in the presence of an antigenic signal. Our results suggest that LIGHT is a costimulatory molecule involved in DC-mediated cellular immune responses.

L15 ANSWER 5 OF 8 SCISEARCH COPYRIGHT 2002 ISI (R)

2000:184672 The Genuine Article (R) Number: 288TL. Modulation of T-cell-mediated immunity in tumor and graft-versus-host disease models through the LIGHT co-stimulatory pathway. Tamada K; Shimozaki K; Chapoval A I; Zhu G F; Sica G; Flies D; Boone T; Hsu H L; Fu Y X; Nagata S; Ni J (Reprint); Chen L P. MAYO CLIN & MAYO FDN, MAYO CLIN & MAYO GRAD SCH MED, DEPT IMMUNOL, 200 1ST ST SW, ROCHESTER, MN 55905 (Reprint); MAYO CLIN & MAYO FDN, MAYO CLIN & MAYO GRAD SCH MED, DEPT IMMUNOL, ROCHESTER, MN 55905; OSAKA UNIV, SCH MED, DEPT GENET, OSAKA, JAPAN; AMGEN INC, THOUSAND OAKS, CA 91320; UNIV CHICAGO, DEPT PATHOL, CHICAGO, IL 60637; HUMAN GENOME SCI INC, ROCKVILLE, MD 20850. NATURE MEDICINE (MAR 2000) Vol. 6, No. 3, pp. 283-289. Publisher: NATURE AMERICA INC. 345 PARK AVE SOUTH, NEW YORK, NY 10010-1707. ISSN: 1078-8956. Pub. country: USA; JAPAN. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB LIGHT was recently described as a member of the tumor necrosis factor (TNF) 'superfamily'. We have isolated a mouse homolog of human LIGHT and investigated its immunoregulatory functions in vitro and in vivo. LIGHT has potent, CD28-independent co-stimulatory activity leading to T-cell growth and secretion of gamma interferon and granulocyte-macrophage colony-stimulating factor. Gene transfer of LIGHT induced an antigen-specific cytolytic T-cell response and therapeutic immunity against established mouse P815 tumor. In contrast, blockade of LIGHT by

administration of **soluble** receptor or antibody led to decreased cell-mediated immunity and ameliorated graft-versus-host disease. Our studies identify a previously unknown T-cell co-stimulatory pathway as a potential therapeutic target.

L15 ANSWER 6 OF 8 SCISEARCH COPYRIGHT 2002 ISI (R)
1999:396027 The Genuine Article (R) Number: 196RW. A newly identified member of tumor necrosis factor receptor superfamily (TR6) suppresses LIGHT-mediated apoptosis. Yu K Y; Kwon B; Ni J; Zhai Y F; Ebner R; Kwon B S (Reprint). INDIANA UNIV, SCH MED, DEPT MICROBIOL & IMMUNOL, 635 BARNHILL DR, INDIANAPOLIS, IN 46202 (Reprint); INDIANA UNIV, SCH MED, DEPT MICROBIOL & IMMUNOL, INDIANAPOLIS, IN 46202; INDIANA UNIV, SCH MED, WALTHER ONCOL CTR, INDIANAPOLIS, IN 46202; WALTHER CANC INST, INDIANAPOLIS, IN 46202; HUMAN GENOME SCI, ROCKVILLE, MD 20850; UNIV ULSAN, DEPT BIOL SCI, ULSAN 680749, SOUTH KOREA; UNIV ULSAN, IMMUNOMODULAT RES CTR, ULSAN 680749, SOUTH KOREA. JOURNAL OF BIOLOGICAL CHEMISTRY (14 MAY 1999) Vol. 274, No. 20, pp. 13733-13736. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. ISSN: 0021-9258. Pub. country: USA; SOUTH KOREA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB TR6 (decoy receptor 3 (DcR3)) is a new member of the tumor necrosis factor receptor (TNFR) family. TR6 mRNA is expressed in lung tissues and colon adenocarcinoma, SW480. In addition, the expression of TR6 mRNA was shown in the endothelial cell line and induced by phorbol 12-myristate 13-acetate/ionomycin in Jurkat T leukemia cells. The open reading frame of TR6 encodes 300 amino acids with a 29-residue signal sequence but no transmembrane region. Using histidine-tagged recombinant TR6, we screened **soluble** forms of TNF-ligand proteins with immunoprecipitation. Here, we demonstrate that TR6 specifically binds two cellular ligands, LIGHT (herpes virus entry mediator (HVEM)-L) and Fas ligand (FasL/CD95L). These bindings were confirmed with HEK 293 EBNA cells transfected with LIGHT cDNA by flow cytometry. TR6 inhibited LIGHT-induced cytotoxicity in HT29 cells. It has been shown that LIGHT triggers apoptosis of various tumor cells including HT29 cells that express both **lymphotoxin beta receptor** (LT beta R) and HVEM/TR2 receptors. Our data suggest that TR6 inhibits the interactions of LIGHT with HVEM/TR2 and LT beta R, thereby suppressing LIGHT-mediated HT29 cell death. Thus, TR6 may play a regulatory role for suppressing in FasL- and LIGHT-mediated cell death.

L15 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2002 ACS
1997:119416 Document No. 126:210816 Activation of the **lymphotoxin .beta. receptor** by crosslinking induces chemokine production and growth arrest in A375 melanoma cells. Degli-Esposti, Mariapia A.; Davis-Smith, Terri; Din, Wenie S.; Smolak, Pamela J.; Goodwin, Raymond G.; Smith, Craig A. (Deps. Biochem. and Molecular Biol., Immunex Corp., Seattle, WA, 98101, USA). J. Immunol., 158(4), 1756-1762 (English) 1997. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB The **lymphotoxin .beta. receptor** (LT.beta.R) was originally described as a transcribed sequence encoded on human chromosome 12p, with homol. to the TNF receptor family. Subsequently, a recombinant LT.beta.R was shown to bind LT.alpha.LT.beta. heteromeric complexes. Here, the authors showed that LT.beta.R is expressed in a variety of tissues and cell lines of monocytic lineage, as well as in fibroblast and human melanoma cell lines. Unlike other members of the TNF receptor family, LT.beta.R is not expressed by peripheral blood T cells. A chimeric fusion protein consisting of the extracellular domain of LT.beta.R fused to the Fc region of human IgG1 was used to develop mAbs against LT.beta.R. Crosslinking LT.beta.R on A375 melanoma cells with these Abs generated an antiproliferative signal. In addn., the IL-8 and RANTES chemokines, early indicators of inflammation, were secreted by the A375 melanoma line and the W138VA13 fibroblast line in response to crosslinking of LT.beta.R. These same activities could be induced by membrane-bound and **sol**. LT.beta. and LT.alpha.LT.beta.

oligomers.

L15 ANSWER 8 OF 8 MEDLINE DUPLICATE 2
96394666 Document Number: 96394666. PubMed ID: 8798772.
Lymphotoxin beta receptor triggering induces activation of the nuclear factor kappaB transcription factor in some cell types. Mackay F; Majeau G R; Hochman P S; Browning J L. (Department of Cell Biology, Biogen Inc., Cambridge, Massachusetts 02142, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Oct 4) 271 (40) 24934-8. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB NFkappaB is a pleiotropic transcription factor capable of activating the expression of a great variety of genes critical for the immunoinflammatory response. Tumor necrosis factor alpha (TNFalpha) and lymphotoxin alpha (LTalpha, originally TNFbeta) are potent nuclear factor kappaB (NFkappaB) activators in various cell types. The LTalpha molecule, in addition to being secreted as a **soluble** trimer, can also form membrane-anchored heterotrimers with the LTbeta chain, another member of the TNF family. The LTalpha1beta2 heterotrimer binds a specific receptor, called the LTbeta receptor (LTbeta-R), which is also a member of the TNF receptor family. Here, we show that engagement of LTbeta-R with a **soluble** form of LTalpha1beta2 or with a specific anti-LTbeta-R agonistic monoclonal antibody CBE11 quickly induces activation of NFkappaB in HT-29 and WiDr human adenocarcinomas. LTbeta-R triggering activates NFkappaB and induces **proliferation** in WI-38 human lung fibroblasts. No NFkappaB activation is observed in human umbilical vein endothelial cells, correlating with the inability of LTbeta-R activation to induce expression of NFkappaB-dependent cell surface adhesion molecules. Thus, like several other members of the TNF receptor family, the LTbeta-R can activate NFkappaB following receptor ligation in some but not all LTbeta-R-positive cells.

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L16 16 "HVEM-FC"

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L17 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2002 ACS
2001:781125 Document No. 135:343309 Ligand p30/LIGHT for HVEM (herpes virus entry mediator) and methods of therapeutic use. Ware, Carl F. (La Jolla Institute for Allergy and Immunology, USA). PCT Int. Appl. WO 2001079496 A2 20011025, 104 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US11857 20010411. PRIORITY: US 2000-524325 20000313; US 2000-549096 20000412.

AB A novel polypeptide ligand, p30, for HVEM (herpes virus entry mediator) and functional variations and fragments thereof are provided. The HVEM ligand is isolated from II-23.D7 cell line, a human CD4+ T cell hybridoma. P30, which can be found as a membrane protein and can function as a cytokine, is also called LIGHT, because this polypeptide is homologous to Lymphotoxins, exhibits Inducible expression, and competes with HSV Glycoprotein D for HVEM, a receptor expressed by T lymphocytes. Because LIGHT can compete with HSV glycoprotein D for HVEM, homo-trimeric sol. forms of this polypeptide can be used to block the entry of herpesvirus

into cells. P30 is useful for modulating immune responses and in inhibiting infection and/or subsequent proliferation by herpesvirus. LIGHT also bind to the lymphotoxin-.beta. receptor (LT.beta.R). The present invention is also based upon the discovery that HVEM polypeptides have an antagonistic effect on inflammation. In particular, HVEM fusion proteins are capable of inhibiting inflammation when administered to a subject. **HVEM-Fc** fusion proteins are also provided.
Methods for treating subjects with lymphoid cell disorders, tumors, autoimmune diseases, inflammatory disorders of those having or suspected of having a herpes virus infection, utilizing p30 and the fusion proteins of the invention, are also provided.

L17 ANSWER 2 OF 5 MEDLINE DUPLICATE 1
2000487952 Document Number: 20491929. PubMed ID: 11035077. Reciprocal expression of the TNF family receptor herpes virus entry mediator and its ligand LIGHT on activated T cells: LIGHT down-regulates its own receptor. Morel Y; Schiano de Colella J M; Harrop J; Deen K C; Holmes S D; Wattam T A; Khandekar S S; Truneh A; Sweet R W; Gastaut J A; Olive D; Costello R T. (Laboratoire d'Immunologie des Tumeurs, Departement d'Hematologie, Institut Paoli Calmettes, Universite de la Mediterranee, Marseille, France.) JOURNAL OF IMMUNOLOGY, (2000 Oct 15) 165 (8) 4397-404. Journal code: IFB. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB The TNF receptor (TNFR) family plays a central role in the development of the immune response. Here we describe the reciprocal regulation of the recently identified TNFR superfamily member herpes virus entry mediator (HVEM) (TR2) and its ligand LIGHT (TL4) on T cells following activation and the mechanism of this process. T cell activation resulted in down-regulation of HVEM and up-regulation of LIGHT, which were both more pronounced in CD8(+) than CD4(+) T lymphocytes. The analysis of HVEM and LIGHT mRNA showed an increase in the steady state level of both mRNAs following stimulation. LIGHT, which was present in cytoplasm of resting T cells, was induced both in cytoplasm and at the cell surface. For HVEM, activation resulted in cellular redistribution, with its disappearance from cell surface. HVEM down-regulation did not rely on de novo protein synthesis, in contrast to the partial dependence of LIGHT induction. Matrix metalloproteinase inhibitors did not modify HVEM expression, but did enhance LIGHT accumulation at the cell surface. However, HVEM down-regulation was partially blocked by a neutralizing mAb to LIGHT or an **HVEM-Fc** fusion protein during activation. As a model, we propose that following stimulation, membrane or secreted LIGHT binds to HVEM and induces receptor down-regulation. Degradation or release of LIGHT by matrix metalloproteinases then contributes to the return to baseline levels for both LIGHT and HVEM. These results reveal a self-regulating ligand/receptor system that contributes to T cell activation through the interaction of T cells with each other and probably with other cells of the immune system.

L17 ANSWER 3 OF 5 MEDLINE DUPLICATE 2
1998438532 Document Number: 98438532. PubMed ID: 9765287. Herpesvirus entry mediator ligand (HVEM-L), a novel ligand for HVEM/TR2, stimulates proliferation of T cells and inhibits HT29 cell growth. Harrop J A; McDonnell P C; Brigham-Burke M; Lyn S D; Minton J; Tan K B; Dede K; Spampanato J; Silverman C; Hensley P; DiPrinzio R; Emery J G; Deen K; Eichman C; Chabot-Fletcher M; Truneh A; Young P R. (Department of Molecular and Cellular Immunology, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania 19406, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Oct 16) 273 (42) 27548-56. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB Herpesvirus entry mediator (HVEM), a member of the tumor necrosis factor (TNF) receptor family, mediates herpesvirus entry into cells during infection. Upon overexpression, HVEM activates NF-kappaB and AP-1 through a TNF receptor-associated factor (TRAF)-mediated mechanism. Using an **HVEM-Fc** fusion protein, we screened soluble forms of novel TNF-related proteins derived from an expressed sequence tag data

base. One of these, which we designated HVEM-L, specifically bound to **HVEM-Fc** with an affinity of 44 nM. This association was confirmed with soluble and membrane forms of both receptor and ligand. HVEM-L mRNA is expressed in spleen, lymph nodes, macrophages, and T cells and encodes a 240-amino acid protein. A soluble, secreted form of the protein stimulates proliferation of T lymphocytes during allogeneic responses, inhibits HT-29 cell growth, and weakly stimulates NF-kappaB-dependent transcription.

L17 ANSWER 4 OF 5 MEDLINE DUPLICATE 3

1998411370 Document Number: 98411370. PubMed ID: 9739048. LIGHT, a novel ligand for lymphotoxin beta receptor and TR2/HVEM induces apoptosis and suppresses in vivo tumor formation via gene transfer. Zhai Y; Guo R; Hsu T L; Yu G L; Ni J; Kwon B S; Jiang G W; Lu J; Tan J; Ugustus M; Carter K; Rojas L; Zhu F; Lincoln C; Endress G; Xing L; Wang S; Oh K O; Gentz R; Ruben S; Lippman M E; Hsieh S L; Yang D. (Human Genome Sciences, Inc., Rockville, Maryland 20850, USA.) JOURNAL OF CLINICAL INVESTIGATION, (1998 Sep 15) 102 (6) 1142-51. Journal code: HS7; 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB LIGHT is a new member of tumor necrosis factor (TNF) cytokine family derived from an activated T cell cDNA library. LIGHT mRNA is highly expressed in splenocytes, activated PBL, CD8(+) tumor infiltrating lymphocytes, granulocytes, and monocytes but not in the thymus and the tumor cells examined. Introduction of LIGHT cDNA into MDA-MB-231 human breast carcinoma caused complete tumor suppression in vivo. Histological examination showed marked neutrophil infiltration and necrosis in LIGHT expressing but not in the parental or the Neo-transfected MDA-MB-231 tumors. Interferon gamma (IFNgamma) dramatically enhances LIGHT-mediated apoptosis. LIGHT protein triggers apoptosis of various tumor cells expressing both lymphotoxin beta receptor (LTbetaR) and TR2/HVEM receptors, and its cytotoxicity can be blocked specifically by addition of a LTbetaR-Fc or a TR2/**HVEM-Fc** fusion protein. However, LIGHT was not cytolytic to the tumor cells that express only the LTbetaR or the TR2/HVEM or hematopoietic cells examined that express only the TR2/HVEM, such as PBL, Jurkat cells, or CD8(+) TIL cells. In contrast, treatment of the activated PBL with LIGHT resulted in release of IFNgamma. Our data suggest that LIGHT triggers distinct biological responses based on the expression patterns of its receptors on the target cells. Thus, LIGHT may play a role in the immune modulation and have a potential value in cancer therapy.

L17 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2002 ACS

1997:220640 Document No. 126:208748 Cloning and expression of cDNA for herpes simplex virus cellular mediator HVEM and pharmaceuticals derived from the protein and cDNA. Spear, Patricia G.; Montgomery, Rebecca I. (Northwestern University, USA; Spear, Patricia G.; Montgomery, Rebecca I.). PCT Int. Appl. WO 9704658 A1 19970213, 57 pp. DESIGNATED STATES: W: CA, US; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US12374 19960726. PRIORITY: US 1995-509024 19950728.

AB The present invention provides isolated and purified polynucleotides that encode HVEM of mammalian origin, expression vectors contg. those polynucleotides, host cells transformed with those expression vectors, a process of making HVEM using those polynucleotides and vectors, and isolated and purified HVEM. Antisense nucleic acids based on the cDNA and HVEM or HVEM derivs. may be used in pharmaceuticals. HeLa cell cDNA encoding HVEM was cloned and sequenced. Based on the DNA sequence anal. indicating that the product is a type I membrane glycoprotein with 3.5 Cys-rich repeats, HVEM is proposed to be a new member of the tumor necrosis factor/nerve growth factor receptor family. CHO-K1 and CHO-ST cell lines resistant to HSV-1 entry become significantly more susceptible when expressing the HVEM cDNA. Anti-HVEM antiserum protected these cells from infection, but the mechanism was not that of preventing binding to the cells. An **HVEM-Fc** fusion protein also inhibited infection of the HVEM-producing recombinant cells.

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L18 4 "HVEM-IG"

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L19 1 DUP REMOVE L18 (3 DUPLICATES REMOVED)

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L19 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
2000219245 Document Number: 20219245. PubMed ID: 10754304. LIGHT, a TNF-like molecule, costimulates T cell proliferation and is required for dendritic cell-mediated allogeneic T cell response. Tamada K; Shimozaki K; Chapoval A I; Zhai Y; Su J; Chen S F; Hsieh S L; Nagata S; Ni J; Chen L. (Department of Immunology, Mayo Graduate and Medical Schools, Mayo Clinic, Rochester, MN 55905, USA.) JOURNAL OF IMMUNOLOGY, (2000 Apr 15) 164 (8) 4105-10. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB LIGHT is a recently identified member of the TNF superfamily and its receptors, herpesvirus entry mediator and lymphotoxin beta receptor, are found in T cells and stromal cells. In this study, we demonstrate that LIGHT is selectively expressed on immature dendritic cells (DCs) generated from human PBMCs. In contrast, LIGHT is not detectable in DCs either freshly isolated from PBMCs or rendered mature in vitro by LPS treatment. Blockade of LIGHT by its soluble receptors, lymphotoxin beta receptor-Ig or **HVEM-Ig**, inhibits the induction of DC-mediated primary allogeneic T cell response. Furthermore, engagement of LIGHT costimulates human T cell proliferation, amplifies the NF-kappaB signaling pathway, and preferentially induces the production of IFN-gamma, but not IL-4, in the presence of an antigenic signal. Our results suggest that LIGHT is a costimulatory molecule involved in DC-mediated cellular immune responses.

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L20 0 "LTBR-FC"

=> s "LTbR-Ig"
L21 0 "LTBR-IG"

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